GENOME EDITING OF IMMUNODEFICIENCY GENES IN ANIMALS

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ABSTRACT

The present invention provides genetically modified animals and cells comprising edited chromosomal sequences encoding immunodeficiency proteins. In particular, the animals or cells are generated using a zinc finger nuclelease-mediated editing process. Also provided are methods of assessing the effects of agents in genetically modified animals and cells comprising edited chromosomal sequences encoding immunodeficiency proteins.
FIG. 1

80bp deletion Exon2 (4469bp - 5276bp)

29bp deletion Exon2 (5245bp - 5273bp)
13bp deletion Exon3 (5754bp- 5766bp)

2bp deletion Exon3 (5766bp – 5767bp)

FIG. 2
GENOME EDITING OF IMMUNODEFIENCY GENES IN ANIMALS

CROSS-REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] The invention generally relates to genetically modified animals or cells comprising at least one edited chromosomal sequence encoding an immunodeficiency protein. In particular, the invention relates to the use of a zinc finger nuclease-mediated process to edit chromosomal sequences encoding immunodeficiency proteins in animals or cells.

BACKGROUND OF THE INVENTION

[0003] The causes of diseases and disorders of the immune system are varied, but genetic variation in certain proteins is the primary cause or contributor to several human immunodeficiency diseases. Mutations in the human RAG 1 or RAG 2 genes cause certain types of Severe Combined Immunodeficiency Disorder (SCID). Ataxia telangiectasia (A-T) (also known as Boder-Sedgwick syndrome or Louis-Bar syndrome) is a rare, neurodegenerative, inherited disease that causes immunodeficiency in 70% of cases and is caused by a defect in the ATM gene. CD45 deficiency is characterized by a markedly decreased level of circulating T-cells and is caused by mutations in the CD45 gene. Specific genetic defects or chromosomal abnormalities have been linked to, or are suspected in many other human immunodeficiencies.

[0004] However, the progress of ongoing research into the causes, specific effects and treatments of these immune system disorders is hampered by the onerous task of developing animal models that incorporate the specific genes suspected of involvement in a given disorder. Conventional methods such as gene knockout technology may be used to edit a particular gene in a potential model organism in order to develop an animal model of particular immunodeficiency. However, gene knockout technology may require months or years to construct and validate the proper knockout models. In addition, genetic editing via gene knockout technology has been reliably developed in only a limited number of organisms such as mice.

[0005] Other animals may be better candidates as model organisms for the study of a given immune system disorder, particularly those that are not well-modeled in mice, or those for which an animal of larger physical size, such as a rat may facilitate experimentation that may requires dissection, in vivo imaging, or isolation of specific cells or organ structures for cellular or molecular studies of these disease or condition.

[0006] A need exists for animals with modification of one or more genes to be used as model organisms in which to study genetic factors in diseases of immunodeficiency. The genetic modifications may include gene knockouts, expression, modified expression, or over-expression of alleles that either cause or contribute to immunodeficiency in humans. Further, a need exists for modification of one or more genes associated with immunodeficiency in a variety of organisms in order to develop appropriate animal models of immune system disorders.

SUMMARY OF THE INVENTION

[0007] One aspect of the present disclosure encompasses a genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein.

[0008] A further aspect provides a non-human embryo comprising at least one RNA molecule encoding a zinc finger nuclease that recognizes a chromosomal sequence encoding an immunodeficiency protein and, optionally, at least one donor polynucleotide comprising a sequence encoding an ortholog of the immunodeficiency protein.

[0009] Another aspect provides an isolated cell comprising at least one edited chromosomal sequence encoding an immunodeficiency protein.

[0010] Yet another aspect encompasses a method for assessing the effect of an agent in an animal. The method comprises contacting a genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein with the agent, and comparing results of a selected parameter to results obtained from contacting a wild-type animal with the same agent. The selected parameter is chosen from (a) rate of elimination of the agent or its metabolite(s); (b) circulatory levels of the agent or its metabolite(s); (c) bioavailability of the agent or its metabolite(s); (d) rate of metabolism of the agent or its metabolite(s); (e) rate of clearance of the agent or its metabolite(s); (f) toxicity of the agent or its metabolite(s); and (g) efficacy of the agent or its metabolite(s).

[0011] Still yet another aspect encompasses a method for assessing the therapeutic potential of an agent in an animal. The method includes contacting a genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein, with the agent and comparing the results of a selected parameter to results obtained from a wild-type animal with no contact with the same agent. The selected parameter may be chosen from a) spontaneous behaviors; b) performance during behavioral testing; c) physiological anomalies; d) abnormalities in tissues or cells; e) biochemical function; and f) molecular structures.

[0012] Other aspects and features of the disclosure are described more thoroughly below.

REFERENCE TO COLOR FIGURES

[0013] The application file contains at least one figure executed in color. Copies of this patent application publica-
tion with color figures will be provided by the Office upon request and payment of the necessary fee.

**BRIEF DESCRIPTION OF THE FIGURES**

**[0014]** FIG. 1 presents the DNA sequences of edited Rag1 loci in two animals. The upper sequence (SEQ ID NO:1) has a 588 by deletion in exon 2, and the lower sequence (SEQ ID NO:2) has a 29 by deletion in exon 2. The exon sequence is shown in green; the target site is presented in yellow, and the deletions are shown in dark blue.

**[0015]** FIG. 2 presents the DNA sequences of edited Rag2 loci in two animals. The upper sequence (SEQ ID NO: 3) has a 13 by deletion in the target sequence in exon 3, and the lower sequence (SEQ ID NO:4) has a 2 by deletion in the target sequence in exon 2. The exon sequence is shown in green; the target site is presented in yellow, and the deletions are shown in dark blue.

**DETAILED DESCRIPTION OF THE INVENTION**

**[0016]** The present disclosure provides a genetically modified animal or animal cell comprising at least one edited chromosomal sequence encoding a protein associated with immunodeficiency. The edited chromosomal sequence may be (1) inactivated, (2) modified, or (3) comprise an integrated sequence. An inactivated chromosomal sequence is altered such that a functional protein is not made. Thus, a genetically modified animal comprising an inactivated chromosomal sequence may be termed a “knock out” or a “conditional knock out.” Similarly, a genetically modified animal comprising an integrated sequence may be termed a “knock in” or a “conditional knock in.” As detailed below, a knock in animal may be a humanized animal. Furthermore, a genetically modified animal comprising a modified chromosomal sequence may comprise a targeted point mutation(s) or other modification such that an altered protein product is produced. The chromosomal sequence encoding the protein associated with immunodeficiency generally is edited using a zinc finger nuclease-mediated process. Briefly, the process comprises introducing into an embryo or cell at least one RNA molecule encoding a targeted zinc finger nuclease and, optionally, at least one accessory polynucleotide. The method further comprises incubating the embryo or cell to allow expression of the zinc finger nuclease, wherein a double-stranded break introduced into the targeted chromosomal sequence by the zinc finger nuclease is repaired by an error-prone non-homologous end-joining DNA repair process or a homology-directed DNA repair process. The method of editing chromosomal sequences encoding a protein associated with immunodeficiency using targeted zinc finger nuclease technology is rapid, precise, and highly efficient.

(I) Genetically Modified Animals

**[0017]** One aspect of the present disclosure provides a genetically modified animal in which at least one chromosomal sequence encoding an immunodeficiency protein has been edited. For example, the edited chromosomal sequence may be inactivated such that the sequence is not transcribed and/or a functional immunodeficiency protein is not produced. Alternatively, the edited chromosomal sequence may be modified such that it codes for an altered immunodeficiency protein. For example, the chromosomal sequence may be modified such that at least one nucleotide is changed and the expressed immunodeficiency protein comprises at least one changed amino acid residue (missense mutation). The chromosomal sequence may be modified to comprise more than one missense mutation such that more than one amino acid is changed. Additionally, the chromosomal sequence may be modified to have a three nucleotide deletion or insertion such that the expressed immunodeficiency protein comprises a single amino acid deletion or insertion, provided such a protein is functional. The modified protein may have altered substrate specificity, altered enzyme activity, altered kinetic rates, and so forth. Furthermore, the edited chromosomal sequence may comprise an integrated sequence and/or a sequence encoding an orthologous protein associated with an immune system disorder. The genetically modified animal disclosed herein may be heterozygous for the edited chromosomal sequence encoding a protein associated with an immune system disorder. Alternatively, the genetically modified animal may be homozygous for the edited chromosomal sequence encoding a protein associated with an immune system disorder.

**[0018]** In one embodiment, the genetically modified animal may comprise at least one inactivated chromosomal sequence encoding an immunodeficiency protein. The inactivated chromosomal sequence may include a deletion mutation (i.e., deletion of one or more nucleotides), an insertion mutation (i.e., insertion of one or more nucleotides), or a nonsense mutation (i.e., substitution of a single nucleotide for another nucleotide such that a stop codon is introduced). As a consequence of the mutation, the targeted chromosomal sequence is inactivated and a functional immunodeficiency protein is not produced. The inactivated chromosomal sequence comprises no exogenously introduced sequence. Such an animal may be termed a “knockout.” Also included herein are genetically modified animals in which two, three, four, five, six, seven, eight, nine, or ten or more chromosomal sequences encoding proteins associated with immune system disorders are inactivated.

**[0019]** In another embodiment, the genetically modified animal may comprise at least one edited chromosomal sequence encoding an orthologous protein associated with an immune system disorder. The edited chromosomal sequence encoding an orthologous immunodeficiency protein may be modified such that it codes for an altered protein. For example, the edited chromosomal sequence encoding an immunodeficiency protein may comprise at least one modification such that an altered version of the protein is produced. In some embodiments, the edited chromosomal sequence comprises at least one modification such that the altered version of the immunodeficiency protein results in an immune system disorder in the animal. In other embodiments, the edited chromosomal sequence encoding an immunodeficiency protein comprises at least one modification such that the altered version of the protein protects against an immune system disorder in the animal. The modification may be a missense mutation in which substitution of one nucleotide for another nucleotide changes the identity of the coded amino acid.

**[0020]** In yet another embodiment, the genetically modified animal may comprise at least one chromosomally integrated sequence. The chromosomally integrated sequence may encode an orthologous immunodeficiency protein, an endogenous immunodeficiency protein, or combinations of both. For example, a sequence encoding an orthologous protein or an endogenous protein may be integrated into a chromosomal sequence encoding a protein such that the chromo-
somal sequence is inactivated, but wherein the exogenous sequence may be expressed. In such a case, the sequence encoding the orthologous protein or endogenous protein may be operably linked to a promoter control sequence. Alternatively, a sequence encoding an orthologous protein or an endogenous protein may be integrated into a chromosomal sequence without affecting expression of a chromosomal sequence. For example, a sequence encoding an immunodeficiency protein may be integrated into a “safe harbor” locus, such as the Rosa26 locus, HPRT locus, or AAV locus. An animal comprising a chromosomally integrated sequence encoding an immunodeficiency protein may be called a “knock-in,” and it should be understood that in certain iterations of the disclosure such an animal may have no selectable marker. The present disclosure also encompasses genetically modified animals in which two, three, four, five, six, seven, eight, nine, or ten or more sequences encoding protein(s) associated with immune system disorders are integrated into the genome.

The chromosomally integrated sequence encoding an immunodeficiency protein may encode the wild type form of the protein. Alternatively, the chromosomally integrated sequence encoding an immunodeficiency protein may comprise at least one modification such that an altered version of the protein is produced. In some embodiments, the chromosomally integrated sequence encoding an immunodeficiency protein comprises at least one modification such that the altered version of the protein produced causes an immune system disorder. In other embodiments, the chromosomally integrated sequence encoding an immunodeficiency protein comprises at least one modification such that the altered version of the protein protects against the development of an immune system disorder.

In an additional embodiment, the genetically modified animal may be a “humanized” animal comprising at least one chromosomally integrated sequence encoding a functional human immunodeficiency-related protein. The functional human immunodeficiency-related protein may have no corresponding ortholog in the genetically modified animal. Alternatively, the wild-type animal from which the genetically modified animal is derived may comprise an ortholog corresponding to the functional human immunodeficiency-related protein. In this case, the orthologous sequence in the “humanized” animal is inactivated such that no functional protein is made and the “humanized” animal comprises at least one chromosomally integrated sequence encoding the human immunodeficiency-related protein. Those of skill in the art appreciate that “humanized” animals may be generated by crossing a knock out animal with a knock in animal comprising the chromosomally integrated sequence.

In yet another embodiment, the genetically modified animal may comprise at least one edited chromosomal sequence encoding an immunodeficiency-related protein such that the expression pattern of the protein is altered. For example, regulatory regions controlling the expression of the protein, such as a promoter or transcription binding site, may be altered such that the immunodeficiency-related protein is over-produced, or the tissue-specific or temporal expression of the protein is altered, or a combination thereof. Alternatively, the expression pattern of the immunodeficiency-related protein may be altered using a conditional knockout system. A non-limiting example of a conditional knockout system includes a Cre-lox recombination system. A Cre-lox recombination system comprises a Cre recombinase enzyme, a site-specific DNA recombinase that can catalyze the recombination of a nucleic acid sequence between specific sites (lox sites) in a nucleic acid molecule. Methods of using this system to produce temporal and tissue specific expression are known in the art. In general, a genetically modified animal is generated with lox sites flanking a chromosomal sequence, such as a chromosomal sequence encoding an immunodeficiency-related protein. The genetically modified animal comprising the lox-flanked chromosomal sequence encoding an immunodeficiency-related protein may then be crossed with another genetically modified animal expressing Cre recombinase. Progeny animals comprising the lox-flanked chromosomal sequence and the Cre recombinase are then produced, and the lox-flanked chromosomal sequence encoding an immunodeficiency-related protein is recombined, leading to deletion or inversion of the chromosomal sequence encoding the protein. Expression of Cre recombinase may be temporarily and conditionally regulated to affect temporarily and conditionally regulated recombination of the chromosomal sequence encoding an immunodeficiency-related protein.

Single-, double- and triple-knock-out animals are expressly contemplated. Exemplary, non-limiting mammalian, e.g., rat chromosomal sequences that can be edited singly or in combination with one or more other proteins relating to immunodeficiency include fumaraylacetate hydratase (FAH), recombination-activating genes-1 (Rag1), recombination-activating genes-2 (Rag2), Forkhead box O1 (Foxo1), DNAPK (dsDNA-dependent protein kinase), and IL2 gamma receptor. In one embodiment, a genetically modified rat may comprise an edited chromosomal sequence encoding fumaraylacetate hydratase gene FAH. A mutation in the fumaraylacetate hydratase may cause severe immunodeficiency. After pretreatment with a urokinase-expressing adenovirus, such rats can be highly engrafted with human hepatocytes from multiple sources, including liver biopsies. Furthermore, human cells could be serially transplanted from primary donors and repopulate the liver for many sequential rounds. The expanded cells are more likely to display typical human drug metabolism. A genetically modified rat that can be highly re-populated with human hepatocytes would have many potential uses in drug development and research applications. Therefore a rat comprising modified FAH may be a useful model system functioning as a robust platform to produce high-quality human hepatocytes for tissue culture, to test the toxicity of drug metabolites and to evaluate pathogens dependent on human liver cells for replication.

Regulated expression of the recombinesse RAG-1 (recombination-activating genes-1) and RAG-2 (recombination-activating genes-2) proteins is generally necessary for generating the vast repertoire of antigen receptors essential for adaptive immunity. In one embodiment, a genetically modified rat may comprise an edited chromosomal sequence encoding protein RAG-1, wherein the edited chromosomal sequence comprises a mutation such that an altered recombinase RAG-1 is produced. The mutation may also be a nonsense mutation in which substitution of one nucleotide for another introduces a stop codon, a deletion mutation in which one or more nucleotides are deleted from the chromosomal sequence, or an insertion mutation in which one or more nucleotides are introduced into the chromosomal sequence. Accordingly, the nonsense, deletion, or insertion mutation “inactivates” the sequence such that folliculin protein is not produced. Thus, a genetically modified rat comprising an inactivated RAG-1 chromosomal sequence may be used as a
model organism for immunodeficiency disease research and human liver cell growth research.

[0026] Foxo1 is a key regulator of Rag1 and Rag2 transcription in primary B cells. Foxo1 directly activated transcription of the Ragl-Rag2 locus throughout early B cell development, and a decrease in Foxo1 protein diminished the Ragl and Rag2 transcription. A genetically modified rat comprising a Foxo1 edited sequence can be used as a model organism providing a research system for cell biology and pathogenesis of these immunodeficiency diseases and for therapeutic interventions.

[0027] In another embodiment, a genetically modified rat may comprise an edited chromosomal sequence encoding DNAPK protein, wherein the edited chromosomal sequence comprises at least one modification such that an altered version of DNAPK protein is produced. Non-Homologous End Joining (NHEJ) is one of the two major pathways of DNA Double Strand Breaks (DSBs) repair. Mutations in human NHEJ genes, such as DNAPK, can lead to immunodeficiency due to its role in V(D)J recombination (also known as somatic recombination) in the immune system. The modification may be a missense mutation in which substitution of one nucleotide for another nucleotide changes the identity of the coded amino acid. The DNAPK coding region may be edited to comprise more than one missense mutation such that more than one amino acid is changed. Additionally, the chromosomal region may be modified to have a three nucleotide deletion or insertion such that the expressed DNAPK protein comprises a single amino acid deletion or insertion, provided such a protein is functional. Those of skill in the art will appreciate that many different modifications are possible in the DNAPK coding region. The modified DNAPK coding region may give rise to a DNAPK protein associated with immunodeficiency. In one embodiment, the genetically modified rat comprising a modified DNAPK chromosomal region may be deficient in repair of replication-induced DSBs.

[0028] The present disclosure also encompasses a genetically modified animal, e.g., a rat, comprising any combination of the above described chromosomal alterations. For example, a genetically modified rat may comprise a modified or inactivated FAH, and/or modified or inactivated Rag1 chromosomal sequence, and/or a modified Rag2 chromosomal sequence; and/or a modified inactivated Foxo1, DNAPK, and/or IL2 gamma receptor. All and any combination of the above described chromosomal alterations may be used for hepatocyte expansion either from human or other sources, which further enables drug metabolism studies, toxicology studies, safety assessment studies, infection disease research, chronic liver disease, acute liver disease, hepatocellular carcinoma, hepatitis, and any other liver infections or diseases.

(a) Immunodeficiency Proteins

[0029] Immunodeficiency proteins are those proteins for which an alteration in activity is linked to an immunodeficiency, which may be the primary or a secondary symptom of an animal disease or condition, preferably a mammalian, e.g., a human disease or condition. Inheritance of the immunodeficiency may be known and of any type, or unknown but suspected of involving a yet unidentified or incompletely identified genetic defect. Non-limiting examples of such human diseases and conditions include combined immunodeficiencies including Severe Combined Immunodeficiency (SCID) including T-B+ SCID and T-B- SCID, X-linked (ye deficiency), Autosomal recessive (Jak3 deficiency), IL7R deficiency, CD45 deficiency RAG 1/2 deficiency, Artemis deficiency, Adenosine deaminase (ADA) deficiency, Reticular dysgenesis, Omenn syndrome, X-linked hyper IgM, CD40 deficiency, Purine nucleoside phosphorylase (PNP) deficiency, MHIC class II deficiency, CD3y or CD3 deficiency, CD8, ZAP-70 deficiency, TAP-1 deficiency, TAP-2 deficiency and Winged Helix Nude (WHN)-deficiency; other well-defined immunodeficiency syndromes Wiskott-Aldrich syndrome, Ataxia-telangiectasia, Ataxia-like syndrome (or Ataxia-telangiectasia like disorder, ATLD), Nijmegen breakage syndrome (NBS), DiGeorge syndrome (or DiGeorge anomaly), immunodeficiency with albinism, Chediak Higashi syndrome, Griscelli syndrome, X-linked lymphoproliferative syndrome, Fanconi anemia, lymphohistiocytosis, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), Autoimmune polyendocrinopathy and ectodermal dysplasia, and X-linked immunodeficiency and ectodermal dysplasia; predominantly antibody deficiencies including X-linked agammaglobulinemia, Autosomal recessive agammaglobulinemia, Ig heavy-chain gene deletions, k Chain deficiency mutations at AR, Selective Ig deficiency (IgG deficiency, IgA deficiency), Antibody deficiency with normal or elevated Ig’s, Common variable immunodeficiency, Transient hypogammaglobulinemia of infancy, and AID deficiency; and congenital defects of phagocytic number and/or function including Severe congenital neutropenia (Kostmann), Cyclic neutropenia, X-linked neutropenia N. Leucocyte adhesion defect, Leucocyte adhesion defect, Rac-2 GTPase defect, Specific granule, Shwachman-Diamond syndrome, Chronic granulomatous disease including X-linked CDG and Autosomal CGD, Neutrophil G-6 PD defect, Myeloperoxidase, and Leucocyte mycobactericidal defects including IFN-γ receptor defectors, STAT-1-defect, Interleukin-12-receptor defect and Interleukin-12-defect; and Bloom’s syndrome, Hypogammaglobulinemia, Job syndrome, Panhypogammaglobulinemia, Britton disease, Asthma, Cohn’s disease (IBD), autoimmune polyglandular syndrome, primary immunodeficiency disease (PID), Ataxia oculomotor apraxia type 1, Ataxia oculomotor apraxia type 2, Gaucher disease, Hartnup disease, Niemann-Pick disease, and Refsum disease.

[0030] Certain immunodeficiencies are known to be caused by a genetic defect which in many instances has been located to a particular gene or set of genes. For example, Ataxia-telangiectasia (AT1) is caused by a defect in the ATM (Ataxia telangiectasia mutated) gene, which encodes a membrane-specific protein kinase responsible for recognizing and repairing DNA errors. (ATLD) is a rare condition with symptoms similar to that seen in AT but typically with a milder clinical course, in which the gene mutated is hMre11, located on chromosome 11q21. In NBS patients, the Nbs1 gene is defective. Chediak-Higashi syndrome is caused by mutations in the LYST gene, which encodes the lysosomal trafficking regulator, involved in the transport of materials into lysosomes. Severe Combined Immune Deficiency (SCID) refers to several types of immunodeficiency diseases of varying severity. SCID-X1 (“Bubble Boy syndrome”, XSCID, XL-SCID) is a known X-linked version of SCID (all other SCID forms identified are autosomal and recessive). SCID-X1 is caused by mutations in the gene for the γ subunit of the interleukin 2 (IL-2) cytokine receptor. ADA-SCID comprises 15 percent of SCID patients, and is due to a mutation in the ADA gene on
chromosome 20. JAK3 Deficiency maps to the Janus kinase 3 gene on chromosome 19. Interleukin-7 receptor a Chain Deficiency is linked to JAK3 proteins, and four other interleukin receptors (IL-2, IL-5, IL-9 and IL-15). RAG1 and RAG2 Deficiencies also lead to SCID. Mutations in RAG1 or 2 also account for about half of human patients exhibiting a rare autoimmune form of SCID called Omenn syndrome. The genes of more than 30 percent of patients diagnosed with SCID remain unidentified although heritability has been shown. Bloom syndrome (BLM; Bloom-Torre-Machacek syndrome), is a rare autosomal recessive chromosomal disorder characterized by short stature, a facial rash and moderate immune deficiency, specifically deficiency in certain immunoglobulin classes, among other symptoms. Bloom syndrome is linked to mutation in the MSH gene, which is a member of the DNA helicase family. DiGeorge syndrome (also known as 22q11.2 deletion syndrome and DiGeorge anomaly) is characterized by a variety of symptoms including recurrent infection and is caused by the deletion of a small piece of chromosome 22, near the middle of the chromosome at q11.2, i.e., on the long arm of one of the pair of chromosomes 22. These examples are but representative and it will be readily understood that many other immunodeficiencies have been sufficiently well studied to have identified a specific genetic defect as an underlying cause.

[0031] An immunodeficiency gene is one in which a mutation causes or is linked to an immunodeficiency disease. Non-limiting examples of human immunodeficiency genes include A2M [alpha-2-macroglobulin]; AANAT [aralkylamine N-acetyltransferase]; ABCA1 [ATP-binding cassette, sub-family A (ABC1), member 1]; ABCA2 [ATP-binding cassette, sub-family A (ABC1), member 2]; ABCA3 [ATP-binding cassette, sub-family A (ABC1), member 3]; ABCA4 [ATP-binding cassette, sub-family A (ABC1), member 4]; ABCB1 [ATP-binding cassette, sub-family B (MDR/ADR), member 1]; ABCB1 [ATP-binding cassette, sub-family C (CFTR/MRP), member 1]; ABCB2 [ATP-binding cassette, sub-family C (CFTR/MRP), member 2]; ABCB3 [ATP-binding cassette, sub-family C (CFTR/MRP), member 3]; ABCB4 [ATP-binding cassette, sub-family C (CFTR/MRP), member 4]; ABCB8 [ATP-binding cassette, sub-family D (ALD), member 2]; ABCB3 [ATP-binding cassette, sub-family D (ALD), member 3]; ABCG1 [ATP-binding cassette, sub-family G (WHITE), member 1]; ABCG2 [ATP-binding cassette, sub-family G (WHITE), member 2]; ABCG5 [ATP-binding cassette, sub-family G (WHITE), member 3]; ABCG8 [ATP-binding cassette, sub-family G (WHITE), member 4]; ABHD2 [hydrolase domain containing 2]; ABLL1 [c-sib oncogene 1, receptor tyrosine kinase]; ABO [ABO blood group (transferrase A, alpha 1-3N-acetylglactosaminyltransferase; transferrase B, alpha 1-3galactosyltransferase)]; ABlP [aminolide binding protein 1 (amine oxidase (copper-containing))]; ACAAA1 [acetyl-Coenzyme A acetyltransferase 1]; ACACA [acetyl-Coenzyme A carboxylase alpha]; ACAN [aggrecan]; ACAT1 [acetyl-Coenzyme A acetyltransferase 1]; ACAT2 [acetyl-Coenzyme A acetyltransferase 2]; ACN5 [aminoregulatory sensitive channel 5, intestinal]; ACE [angiotensin I converting enzyme (peptidyl-dipeptidase A)]; ACE2 [angiotensin I converting enzyme (peptidyl-dipeptidase A)]; ACEH [acetylecholinkinase (Y1 blood group)]; ACT1Y [ATP citrate lyase]; ACOT9 [acetyl-CoA thioesterase 3]; ACOX1 [acetyl-Coenzyme A oxidase 1, palmitoyl]; ACP1 [acid phosphatase 1, soluble]; ACP2 [acid phosphatase 2, lysosomal]; ACP5 [acid phosphatase 5, tarettate resistant]; ACPP [acid phosphatase, prostate]; ACSL3 [acyl-CoA synthetase long-chain family member 3]; ACSM3 [acyl-CoA synthetase medium-chain family member 3]; ACT1A [actin, alpha 1, skeletal muscle]; ACT2A [actin, alpha 2, smooth muscle, aorta]; ACTB [actin, beta]; ACTC1 [actin, alpha, cardiac muscle 1]; AC1G1 [actin, gamma 1]; ACTN1 [actin, alpha 1]; ACTN2 [actin, alpha 2]; ACTN4 [actin, alpha 4]; ACTR2 [ARP2 actin-related protein 2 homolog (yeast)]; ACVR1 [activin A receptor, type I]; ACVR1B [activin A receptor, type II]; ACVR1L [activin A receptor type II-like 1]; ACY1 [aminooxycyclase 1]; ADA [adenosine deaminase]; ADAM10 [ADAM metallopeptidase domain 10]; ADAM12 [ADAM metallopeptidase domain 12]; ADAM17 [ADAM metallopeptidase domain 17]; ADAM23 [ADAM metallopeptidase domain 23]; ADAM33 [ADAM metallopeptidase domain 33]; ADAM8 [ADAM metallopeptidase domain 8]; ADAMS [ADAM metallopeptidase domain 9 (meltrin gamma)]; ADAMTS1 [ADAM metallopeptidase with thrombospondin type 1 motif, 1]; ADAMTS12 [ADAM metallopeptidase with thrombospondin type 1 motif, 12]; ADAMTS13 [ADAM metallopeptidase with thrombospondin type 1 motif, 13]; ADAMTS15 [ADAM metallopeptidase with thrombospondin type 1 motif, 15]; ADAMTS11 [ADAMTS-like 1]; ADAMTS4 [ADAMTS-like 4]; ADAR [adenosine deaminase, RNA-specific]; ADCY1 [adenylate cyclase 1 (brain)]; ADCY10 [adenylate cyclase 10 (soluble)]; ADCY3 [adenylate cyclase 3]; ADCY9 [adenylate cyclase 9]; ADCYAPI [adenylyl cyclase activating polypeptide 1 (putitury)]; ADCYAPIR1 [adenylate cyclase activating polypeptide 1 (putitury) receptor type I]; ADD1 [aducin 1 (alpha)]; ADD15 [alcohol dehydrogenase 5 (class III), chi polypeptide]; ADIPQ [adiponectin, C1Q and collagen domain containing]; ADIPOR1 [adiponectin receptor 1]; AKD [adenosine kinase]; ADN [adenomodulin]; ADORA1 [adenosine A1 receptor]; ADORA2A [adenosine A2a receptor]; ADORA2B [adenosine A2b receptor]; ADORA3 [adenosine A3 receptor]; ADRA1B [adrennergic, alpha-1B, receptor]; ADRA2A [adrennergic, alpha-2A, receptor]; ADRA2B [adrennergic, alpha-2b, receptor]; ADRB1 [adrennergic, beta-1, receptor]; ADRB2 [adrennergic, beta-2, receptor, surface]; ADSL [adenosylcuccinate lyase]; ADSS [adenosylcuccinate synthase]; AE1 [AE binding protein 1]; AFP [alpha-fetoprotein]; AGER [advanced glycosylation endproduct-specific receptor]; AGMAT [agmatine ureohydrolase (agmatinase)]; AGPS [alkylglycerone phosphate synthase]; AGRN [arginin]; GRP [argin related protein homolog (mouse)]; AGT [angiotensinogen (serpin peptidase inhibitor, clade A, member 8)]; AGTR1 [angiotensin II receptor, type 1]; AGTR2 [angiotensin II receptor, type 2]; AHOY [adenosylhomocysteinase]; AHII [Abelson helper integration site 1]; AHR [aryl hydrocarbon receptor]; AIHS [alpha hemoglobin stabilizing protein]; AICDA [activation-induced cytidine deaminase]; AIDA [axin interactor, doralization associated]; AIMP1 [aminooxy 1rRNA synthetase complex-interacting multifunctional protein]; AIRE [autoimmune regulator]; AK1 [adenylate kinase 1]; AK2 [adenylate kinase 2]; AKR1A1 [aldo-keto reductase family 1, member A1 (aldehyde reductase)]; AKR1B1 [aldo-keto reductase family 1, member B1 (aldo reductase)]; AKR1C3 [aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type 1)]; AKT1 [v-akt murine thymoma viral oncogene homolog 1]; AKT2 [v-akt murine thymoma viral oncogene homolog 2]; AKT3 [v-akt murine thymoma viral oncogene homolog 3];
receptor, type II (serine/threonine kinase); BPI [bactericidal/permeability-increasing protein]; BRCA1 [breast cancer 1, early onset]; BRCA2 [breast cancer 2, early onset]; BRCC3 [BRCA1/BRCA2-containing complex, subunit 3]; BRD8 [bromodomain containing 8]; BRIP1 [BRCA1 interacting protein C-terminal helicase 1]; BSG [basigin (Ok blood group)]; BSN [basoon (presynaptic cytomatrix protein)]; Bsx [brain-specific homeobox]; BTD [biodemidase]; BTK [ Bruton agammaglobulinemia tyrosine kinase]; BTLA [B and T lymphocyte associated]; BTNL2 [bputrophilin-like 2 (MHC class II associated)]; BTRC [beta-transducin repeat containing]; C10orf6 [chromosome 10 open reading frame 67]; C11orf90 [chromosome 11 open reading frame 30]; C11orf58 [chromosome 11 open reading frame 58]; C13orf23 [chromosome 13 open reading frame 23]; C13orf31 [chromosome 13 open reading frame 31]; C15orf2 [chromosome 15 open reading frame 2]; C16orf75 [chromosome 16 open reading frame 75]; C19orf10 [chromosome 19 open reading frame 10]; C1QA [component complement 1, q subcomponent, A chain]; C1QB [component complement 1, q subcomponent, B chain]; C1QC [component complement 1, q subcomponent, C chain]; C1QTNF5 [C1q and tumor necrosis factor related protein 5]; C1R [component complement 1, r subcomponent]; C1S [component complement 1, s subcomponent]; C2 [component complement 2]; C2orf29 [chromosome 20 open reading frame 29]; C21orf33 [chromosome 21 open reading frame 33]; C3 [component complement 3]; C3AR1 [component complement 3a receptor 1]; C3orf27 [chromosome 3 open reading frame 27]; C4A [component complement 4A (Rodgers blood group)]; C4B [component complement 4B (Chido blood group)]; C4BPA [component complement 4 binding protein, alpha]; C4BPB [component complement 4 binding protein, beta]; C5 [component complement 5]; C5AR1 [component complement 5a receptor 1]; C5orf56 [chromosome 5 open reading frame 56]; C5orf62 [chromosome 5 open reading frame 62]; C6 [component complement 6]; C6orf142 [chromosome 6 open reading frame 142]; C6orf25 [chromosome 6 open reading frame 25]; C7 [component complement 7]; C7orf72 [chromosome 7 open reading frame 72]; C8A [component complement 8, alpha polypeptide]; C8B [component complement 8, beta polypeptide]; C8G [component complement 8, gamma polypeptide]; C8orf8 [chromosome 8 open reading frame 38]; C9 [component complement 9]; CA2 [carboxic anhydrase II]; CA6 [carboxic anhydrase VI]; CA8 [carboxic anhydrase VIII]; CA9 [carboxic anhydrase IX]; CABIN1 [calcineurin binding protein 1]; CACNA1C [calcium channel, voltage-dependent, L type, alpha 1C subunit]; CACNA1S [calcium channel, voltage-dependent, L type, alpha 1S subunit]; CAD [cambamyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydropyrimidase]; CALB1 [calcibindin 1, 28 kDa]; CALB2 [calcibindin 2]; CALCA [calcitonin-related polypeptide alpha]; CALCR [calcitonin receptor-like]; CALD1 [calcidemion 1]; CALM1 [calmodulin 1 (phosphorylase kinase, delta)]; CALM2 [calmodulin 2 (phosphorylase kinase, delta)]; CALM3 [calmodulin 3 (phosphorylase kinase, delta)]; CALR [calreticulin]; CAMK2G [calcium/calmodulin-dependent protein kinase II gamma]; CAMP [cathelicidin antimicrobial peptide]; CANT1 [calcium activated nucleotide 1]; CANX [canelxin]; CAPN1 [calpain 1, (mu1) large subunit]; CARD10 [caspase recruitment domain family, member 10]; CARD16 [caspase recruitment domain family, member 16]; CARD8 [caspase recruitment domain family, member 8]; CARD5 [caspase recruitment domain family, member 9]; CASP1 [caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, converted)]; CASP10 [caspase 10, apoptosis-related cysteine peptidase]; CASP2 [caspase 2, apoptosis-related cysteine peptidase]; CASP3 [caspase 3, apoptosis-related cysteine peptidase]; CASP5 [caspase 5, apoptosis-related cysteine peptidase]; CASP6 [caspase 6, apoptosis-related cysteine peptidase]; CASP7 [caspase 7, apoptosis-related cysteine peptidase]; CASP8 [caspase 8, apoptosis-related cysteine peptidase]; CASP8AP2 [caspase 8 associated protein 2]; CASP9 [caspase 9, apoptosis-related cysteine peptidase]; CASR [calcium-sensing receptor]; CAST [calpastatin]; CAT [cathepsin]; CAV1 [caveolin 1, caveole protein, 22 kDa]; CAV2 [caveolin 2]; CBL [Cas-B-c-M (murine) ectopic retroviral transforming sequence]; CBS [cystathionine-beta-synthase]; CBX5 [chromobox homolog 5 (HP1 alpha homolog, Drosophila)]; CC2D2A [coiled-coil and C2 domain containing 2A]; CCBP2 [chemokine binding protein 2]; CCDC14A [coiled-coil domain containing 14A]; CCDC14B [coiled-coil domain containing 14AB]; CCDC68 [coiled-coil domain containing 68]; CCK [cholecystokinin]; CCL1 [chemokine (C-C motif) ligand 1]; CCL11 [chemokine (C-C motif) ligand 11]; CCL13 [chemokine (C-C motif) ligand 13]; CCL14 [chemokine (C-C motif) ligand 14]; CCL17 [chemokine (C-C motif) ligand 17]; CCL18 [chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)]; CCL19 [chemokine (C-C motif) ligand 19]; CCL2 [chemokine (C-C motif) ligand 2]; CCL20 [chemokine (C-C motif) ligand 20]; CCL21 [chemokine (C-C motif) ligand 21]; CCL22 [chemokine (C-C motif) ligand 22]; CCL24 [chemokine (C-C motif) ligand 24]; CCL25 [chemokine (C-C motif) ligand 25]; CCL26 [chemokine (C-C motif) ligand 26]; CCL27 [chemokine (C-C motif) ligand 27]; CCL28 [chemokine (C-C motif) ligand 28]; CCL3 [chemokine (C-C motif) ligand 3]; CCL4 [chemokine (C-C motif) ligand 4]; CCL4L1 [chemokine (C-C motif) ligand 4 like 1]; CCL5 [chemokine (C-C motif) ligand 5]; CCL7 [chemokine (C-C motif) ligand 7]; CCL8 [chemokine (C-C motif) ligand 8]; CCNA1 [cyclin A1]; CCNA2 [cyclin A2]; CCNB1 [cyclin B1]; CCNB2 [cyclin B2]; CCNC [cyclin C]; CCND1 [cyclin D1]; CCND2 [cyclin D2]; CCND3 [cyclin D3]; CCNE1 [cyclin E1]; CCNG1 [cyclin G1]; CCNH [cyclin H]; CCNT1 [cyclin T1]; CCNT2 [cyclin T2]; CCNY [cyclin Y]; CCR1 [chemokine (C-C motif) receptor 1]; CCR2 [chemokine (C-C motif) receptor 2]; CCR3 [chemokine (C-C motif) receptor 3]; CCR4 [chemokine (C-C motif) receptor 4]; CCR5 [chemokine (C-C motif) receptor 5]; CCR6 [chemokine (C-C motif) receptor 6]; CCR7 [chemokine (C-C motif) receptor 7]; CCR8 [chemokine (C-C motif) receptor 8]; CCR9 [chemokine (C-C motif) receptor 9]; CCR11 [chemokine (C-C motif) receptor-like 1]; CD14 [CD14 molecule]; CD151 [CD151 molecule (Raph blood group)]; CD160 [CD160 molecule]; CD163 [CD163 molecule]; CD180 [CD180 molecule]; CD19 [CD19 molecule]; CD1A [CD1a molecule]; CD1B [CD1b molecule]; CD1C [CD1e molecule]; CD1D [CD1d molecule]; CD2 [CD2 molecule]; CD200 [CD200 molecule]; CD207 [CD207 molecule, langerin]; CD209 [CD209 molecule]; CD22 [CD22 molecule]; CD26 [CD26 molecule]; CD24 [CD24 molecule]; CD244 [CD244 molecule, natural killer cell receptor 2B4]; CD247 [CD247 molecule]; CD27 [CD27 molecule]; CD274 [CD274 molecule]; CD28 [CD28 molecule]; CD2AP [CD2-associated protein]; CD300LF [CD300 molecule-like family mem-
CD34 [CD34 molecule (thrombopoietin receptor)]; CD36 [CD36 molecule (thrombopoietin receptor)]; CD37 [CD37 molecule]; CD38 [CD38 molecule]; CD3E [CD3e molecule, epsilon (CD3-TCR complex)]; CD4 [CD4 molecule]; CD45 [CD45 molecule].

Decay accelerating factor for complement (Cramer blood group); CD55 [CD55 molecule, complement regulatory protein]; CD63 [CD63 molecule]; CD68 [CD68 molecule]; CD69 [CD69 molecule]; CD7 [CD7 molecule]; CD70 [CD70 molecule]; CD72 [CD72 molecule]; CD74 [CD74 molecule, major histocompatibility complex, class II invariant chain]; CD79A [CD79a molecule, immunoglobulin-associated alpha]; CD79B [CD79b molecule, immunoglobulin-associated beta]; CD80 [CD80 molecule]; CD81 [CD81 molecule]; CD82 [CD82 molecule]; CD83 [CD83 molecule]; CD86 [CD86 molecule]; CD88 [CD88 molecule]; CD89 [CD9 molecule]; CD93 [CD93 molecule]; CD97 [CD97 molecule]; CDC20 [cell division cycle 20 homolog (S. cerevisiae)]; CDC25A [cell division cycle 25 homolog A (S. pombe)]; CDC25B [cell division cycle 25 homolog B (S. pombe)]; CDC25C [cell division cycle 25 homolog C (S. pombe)]; CDC42 [cell division cycle 42 (GTP binding protein, 25 kDa)]; CDC45 [CDC45 cell division cycle 45 homolog (S. cerevisiae)]; CDC5L [CDC5 cell division cycle 5-like (S. pombe)]; CDC6 [cell division cycle 6 homolog (S. cerevisiae)]; CDC7 [cell division cycle 7 homolog (S. cerevisiae)]; CDH1 [cadherin 1, type 1, E-cadherin (epithelial)]; CDH2 [cadherin 2, type 1, N-cadherin (neural)]; CDH6 [cadherin 6]; CDH13 [cadherin 13, type 3, P-cadherin (placental)]; CDH5 [cadherin 5, type 2 (vascular endothelium)]; CDPTD [CDP-diacylglycerol-inositol-3-phosphatidylinositol synthase]; CDK1 [cyclin-dependent kinase 1]; CDK2 [cyclin-dependent kinase 2]; CDK4 [cyclin-dependent kinase 4]; CDK5 [cyclin-dependent kinase 5]; CDK5R1 [cyclin-dependent kinase 5, regulatory subunit 1 (p35)]; CDK7 [cyclin-dependent kinase 7]; CDK9 [cyclin-dependent kinase 9]; CDKAL1 [CDK5 regulatory subunit associated protein 1-like 1]; CDKN1A [cyclin-dependent kinase inhibitor 1A (p21, Cip1)]; CDKN1B [cyclin-dependent kinase inhibitor 1B (p27, Kip1)]; CDKN1C [cyclin-dependent kinase inhibitor 1C (p57, Kip2)]; CDKN2A [cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4, 4.8 kDa)]; CDKN2B [cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4, 4.8 kDa)]; CDKN3 [cyclin-dependent kinase inhibitor 3]; CDR2 [cerebellar degeneration-related protein 2, 6.2 kDa]; CDT1 [chromatin licensing and DNA replication factor 1]; CDX2 [caudal type homeobox 2]; CEACAM1 [carcinoembryonic antigen-related cell adhesion molecule 1 (bilary glycoprotein)]; CEACAM3 [carcinoembryonic antigen-related cell adhesion molecule 3]; CEACAM5 [carcinoembryonic antigen-related cell adhesion molecule 5]; CEACAM6 [carcinoembryonic antigen-related cell adhesion molecule 6 (non-specific cross reacting antigen)]; CEACAM7 [carcinoembryonic antigen-related cell adhesion molecule 7]; CEBPB [CCAAT/enhancer binding protein (C/EBP), beta]; CEL [carboxyl ester lipase (bile salt-stimulated lipase)]; CENP[centromere protein]; CENPV [centromere protein V]; CEP290 [centrosomal protein 290 kDa]; CERK [ceramide kinase]; CETF [cholesterol ester transfer protein, plasma]; CFB [complement factor B]; CFD [complement factor D (adipin)]; CFD1 [complement factor D (adipin)]; CFD1P1 [complement factor D (adipin)]; CFH [complement factor H]; CFHR1 [complement factor H-related 1]; CFHR3 [complement factor H-related 3]; CFI [complement factor I]; CFL1 [cofilin 1 (non-muscle)]; CFL2 [cofilin 2 (muscle)]; CFLAR [CASP8 and FADD-like apoptosis regulator]; CFP [complement factor properdin]; CFTR [cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7)]; CGA [glycoprotein hormones, alpha polypeptide]; CGB [chorionic gonadotropin, beta polypeptide]; CG5 [chorionic gonadotropin, beta polypeptide 5]; CHAD [chondroadherin]; CHAF1A [chromatin assembly factor 1, subunit A (p50)]; CHAF1B [chromatin assembly factor 1, subunit B (p60)]; CHAT [choline acetyltransferase]; CHD2 [chromodomain helicase DNA binding protein 2]; CHD7 [chromodomain helicase DNA binding protein 7]; CHEK1 [CHK1 checkpoint homolog (S. pombe)]; CHEK2 [CHK2 checkpoint homolog (S. pombe)]; CHK3 [CHK3 checkpoint homolog (S. pombe)]; CHGB [chromogranin A (parathyroid secretory protein 1)]; CHGB [chromogranin B (secretogranin 1)]; CHIL1 [chitinase 3-like 1 (cartilage glycoprotein-39)]; CHAI [chitinase, acidic]; CHIT1 [chitinase 1 (chitotriosidase)]; CHKA [chitinase alpha]; ACHM [chondroderma-like (Rab escort protein 2)]; CHIRD [chirin]; CHIRL1 [chirin-like 1]; CHRM1 [cholinergic receptor, muscarinic 1]; CHRM2 [cholinergic receptor, muscarinic 2]; CITRM3 [cholinergic receptor, muscarinic 3]; CHRNA3 [cholinergic receptor, nicotinic, alpha 3]; CHRNA4 [cholinergic receptor, nicotinic, alpha 4]; CHRNA7 [cholinergic receptor, nicotinic, alpha 7]; CHUK [conserved helix-loop-helix ubiquitous kinase]; CIB1 [calcin and integrin binding 1 (calmyrin)]; CITA [class II, major histocompatibility complex, transactivator]; CILP [cartilage intermediate layer protein, nucleotide pyrophosphohydrolase]; CISH [cytokine inducible SH2-containing protein]; CKB [creatinine kinase, brain]; CKLF [chemokine-like factor]; CKM [creatinine kinase, muscle]; CLC [Churcot-Leyden crystal protein]; CLCA1 [chloride channel accessory 1]; CLCN1 [chloride channel 1, skeletal muscle]; CLCN3 [chloride channel 3]; CLDN1 [claudin 1]; CLDN11 [claudin 11]; CLDN14 [claudin 14]; CLDN16 [claudin 16]; CLDN19 [claudin 19]; CLDN2 [claudin 2]; CLDN3 [claudin 3]; CLDN4 [claudin 4]; CLDN5 [claudin 5]; CLDN7 [claudin 7]; CLDN8 [claudin 8]; CLEC12A [C-type lectin domain family 12, member A]; CLEC16A [C-type lectin domain family 16, member A]; CLEC4A [C-type lectin domain family 4, member A]; CLEC4D [C-type lectin domain family 4, member D]; CLEC4M [C-type lectin domain family 4, member M]; CLEC7A [C-type lectin domain family 7, member A]; CLEC12P [C-type lectin domain containing linker protein 2]; CLK2 [Cdc-like kinase 2]; CLSPN [clasp homolog ( Xenopus laevis)]; CLSTN2 [calysteginin 2]; CLTCL1 [clathrin, heavy chain-like 1]; CLU [clusterin]; CMA1 [chymase 1, mast cell]; CMKLR1 [chemokine-like receptor 1]; CNBP [CCCH-type zinc finger, nucleic acid binding protein]; CNPD2 [CNDP dipetidase 2 (metallopeptidase M20 family)]; CNN1 [calpain 1, basic, smooth muscle]; CNP [2',3'-cyclic nucleotide 3' phosphodiesterase]; CNN1 [cannabinoid receptor 1 (brain)]; CNN2 [cannabinoid receptor 2 (macrophage)]; CNF [ciliary neurotrophic factor]; CNTN2 [contactin 2 (axonal)]; COG1 [component of oligomeric golgi complex 1]; COG2 [component of oligomeric golgi complex 2]; COIL [collin]; COL1A1 [collagen, type XVII, alpha 1]; COL1A2 [collagen, type X, alpha 2]; COL17A1 [collagen, type XVII, alpha 1];
COL1A1 [collagen, type I, alpha 1]; COL1A2 [collagen, type I, alpha 2]; COL2A1 [collagen, type II, alpha 1]; COL3A1 [collagen, type III, alpha 1]; COL4A1 [collagen, type IV, alpha 1]; COL4A3 [collagen, type IV, alpha 3 (Goodpasture antigen)]; COL4A4 [collagen, type IV, alpha 4]; COL4A5 [collagen, type IV, alpha 5]; COL4A6 [collagen, type IV, alpha 6]; COL5A1 [collagen, type V, alpha 1]; COL5A2 [collagen, type V, alpha 2]; COL6A1 [collagen, type VI, alpha 1]; COL6A2 [collagen, type VI, alpha 2]; COL6A3 [collagen, type VI, alpha 3]; COL7A1 [collagen, type VII, alpha 1]; COL8A2 [collagen, type VIII, alpha 2]; COL9A1 [collagen, type IX, alpha 1]; COMT [catechol-O-methyltransferase]; COOQ [coenzyme Q homolog, mitochondrial transferase (S. cerevisiae)]; COQ7 [coenzyme Q7 homolog, ubiquinone (yeast)]; CORO1A [coronin, actin binding protein, 1A]; COX10 [COX10 homolog, cytochrome c oxidase assembly protein, heme A; farnesyltransferase (yeast)]; COX15 [COX15 homolog, cytochrome c oxidase assembly protein (yeast)]; COX5A [cytochrome c oxidase subunit Va]; COX8A [cytochrome c oxidase subunit VIIIa (ubiquitous)]; CP [ceruloplasmin (ferroxidase)]; CPA1 [carboxypeptidase A1 (pancreatic)]; CPB2 [carboxypeptidase B2 (plasma)]; CPN1 [carboxypeptidase N, polypeptide 1]; CPDX [coproporphyrinogen oxidase]; CPS1 [carbamoyl-phosphate synthetase 1, mitochondrial]; CPT2 [carnitine palmitoyltransferase 2]; CR1 [complement component 3b (3b) receptor 1 (Knops blood group)]; CR2 [complement component 3d (Epstein Barr virus receptor) 2]; CRAT [carnitine O-acetyltransferase]; CRB1 [brunn homolog 1 (Drosophila)]; CREB1 [cAMP responsive element binding protein 1]; CREBBP [CREB binding protein]; CREM [cAMP responsive element modulator]; CRH1 [corticotropin releasing hormone receptor 1]; CRHR1 [corticotropin releasing hormone receptor 1]; CRHR2 [corticotropin releasing hormone receptor 2]; CRK [v-kr sarcoma virus CT10 oncogene homolog (avian)]; CRKL [v-kr sarcoma virus CT10 oncogene homolog (avian-like)]; CRLF2 [cytokine receptor-like factor 2]; CRLF3 [cytokine receptor-like factor 3]; CRONT [carnitine O-acetyltransferase]; CRP [C-reactive protein, pentraxin-related]; CR1 [complement C1r/C1s, O-glycoprotein]; CRYAA [crystallin, alpha A]; CRYAB [crystallin, alpha B]; CS [citrate synthase]; CSF1 [colony stimulating factor 1 (macrophage)]; CSF1R [colony stimulating factor 1 receptor]; CSF2 [colony stimulating factor 2 (granulocyte-macrophage)]; CSF2RB [colony stimulating factor 2 receptor, beta, low-affinity (granulocyte-macrophage)]; CSF3 [colony stimulating factor 3 (granulocyte)]; CSF3R [colony stimulating factor 3 receptor (granulocyte)]; CSK [c-Src tyrosine kinase]; CSMD3 [CUB and Sushi multiple domains 3]; CSN3 [c notion alpha 1]; CSN2 [c notion beta]; CSNK1A1 [casein kinase 1, alpha 1]; CSNK2A1 [casein kinase 2, alpha 1 polypeptide]; CSNK2B [casein kinase 2, beta polypeptide]; CSPG4 [chondroitin sulfate proteoglycan 4]; CST3 [cystatin C]; CST8 [cystatin 8 (cystatin-related epidermal specific)]; CSTA [cystatin A (steflin A)]; CSTB [cystatin B (steflin B)]; CTAGE1 [cutaneous T-cell lymphoma-associated antigen 1]; CT1F [cardiotrophin 1]; CTGF [connective tissue growth factor]; CTI [cytostatin (cystatinine gamma-L-lyase)]; CTLA4 [cytotoxic T-lymphocyte-associated antigen 4]; CTNNAL1 [catenin (cadherin-associated protein), alpha 1, 102 kDa]; CTNNA3 [catenin (cadherin-associated protein), alpha 3]; CTNNAL1 [catenin (cadherin-associated protein), alpha-like 1]; CTNNB1 [catenin (cadherin-associated protein), beta 1, 88 kDa]; CTNND1 [catenin (cadherin-associated protein), delta 1]; CTNS [cystinosin, nephropathic]; CTRL [chymotrypsin-like]; CTSB [cathepsin B]; CTSC [cathepsin C]; CTSD [cathepsin D]; CTSE [cathepsin E]; CTSG [cathepsin G]; CTSH [cathepsin H]; CTSK [cathepsin K]; CTSL1 [cathepsin L1]; CTTN [catractin]; CUL1 [cullin 1]; CUL2 [cullin 2]; CUL4A [cullin 4A]; CUL5 [cullin 5]; CUL5C1 [chimomale (C−X−C motif) ligand 1]; CXCR1 [chimomale (C−X−C motif) receptor 1]; CXADR [crossocke virus and adenovirus receptor]; CXCL1 [chimomale (C−X−C motif) ligand 1 (melenoma growth stimulating activity, alpha)]; CXCL10 [chimomale (C−X−C motif) ligand 10]; CXCL11 [chimomale (C−X−C motif) ligand 11]; CXCL12 [chimomale (C−X−C motif) ligand 12 (stromal cell-derived factor 1)]; CXCL13 [chimomale (C−X−C motif) ligand 13]; CXCL15 [chimomale (C−X−C motif) ligand 5]; CXCL6 [chimomale (C−X−C motif) ligand 6 (granulocyte chemotactic protein 2)]; CXCL9 [chimomale (C−X−C motif) ligand 9]; CXCR1 [chimomale (C−X−C motif) receptor 1]; CXCR2 [chimomale (C−X−C motif) receptor 2]; CXCR3 [chimomale (C−X−C motif) receptor 3]; CXCR4 [chimomale (C−X−C motif) receptor 4]; CXCR5 [chimomale (C−X−C motif) receptor 5]; CXCR6 [chimomale (C−X−C motif) receptor 6]; CXCR7 [chimomale (C−X−C motif) receptor 7]; CXorf40A [chromosome X open reading frame 40A]; CYB5A [cytochrome b5 type A (microsomal)]; CYB5R3 [cytochrome b5 reductase 3]; CYBA [cytochrome b-245, alpha polypeptide]; CYBB [cytochrome b-245, beta polypeptide]; CYC1 [cytochrome c-1]; CYCS [cytochrome c, somatic]; CYFIP2 [cytoplasmic FMR1 interacting protein 2]; CYP11A1 [cytochrome P450, family 11, subfamily A, polypeptide 1]; CYP11B1 [cytochrome P450, family 11, subfamily B, polypeptide 1]; CYP11B2 [cytochrome P450, family 11, subfamily B, polypeptide 2]; CYPI7A1 [cytochrome P450, family 17, subfamily A, polypeptide 1]; CYPI9A1 [cytochrome P450, family 19, subfamily A, polypeptide 1]; CYPIA1 [cytochrome P450, family 1, subfamily A, polypeptide 1]; CYPIA2 [cytochrome P450, family 1, subfamily A, polypeptide 2]; CYPIB1 [cytochrome P450, family 1, subfamily B, polypeptide 1]; CYPIA2 [cytochrome P450, family 21, subfamily A, polypeptide 2]; CYPIA4 [cytochrome P450, family 24, subfamily A, polypeptide 1]; CYPIA1 [cytochrome P450, family 27, subfamily A, polypeptide 1]; CYPIB7 [cytochrome P450, family 27, subfamily B, polypeptide 1]; CYPIA2 [cytochrome P450, family 50, subfamily A, polypeptide 6]; CYPIB6 [cytochrome P450, family 2, subfamily B, polypeptide 6]; CYPIB7 [cytochrome P450, family 2, subfamily C, polypeptide 19]; CYPIB8 [cytochrome P450, family 2, subfamily C, polypeptide 8]; CYPIB9 [cytochrome P450, family 2, subfamily C, polypeptide 9]; CYPIB2 [cytochrome P450, family 2, subfamily D, polypeptide 6]; CYPIE [cytochrome P450, family 50, subfamily E, polypeptide 1]; CYPIF2 [cytochrome P450, family 2, subfamily F, polypeptide 1]; CYPIR1 [cytochrome P450, family 2, subfamily R, polypeptide 1]; CYPIA4 [cytochrome P450, family 3, subfamily A, polypeptide 4]; CYPIA5 [cytochrome P450, family 3, subfamily A, polypeptide 5]; CYPIF3 [cytochrome P450, family 4, subfamily F, polypeptide 3]; CYPIA1 [cytochrome P450, family 51, subfamily A, polypeptide 1]; CYPIA1 [cytochrome P450, family 7, subfamily A, polypeptide 1]; CYR61 [cytisine-rich, angiogenec
inducer, 61]; CYSLTR1 [cysteiny1 leukotriene receptor 1]; CYSLTR2 [cysteiny1 leukotriene receptor 2]; DAO [D-amino-acid oxidase]; DAOA [D-amino acid oxidase activator]; DAP3 [death associated protein 3]; DAPK1 [death associated protein kinase 1]; DARC [Duffy blood group, chemokine receptor]; DAZ1 [deleted in azoospermia 1]; DBH [dopamine beta-hydroxylase (dopamine beta-monoxygenase)]; DCK [deoxycooptidylate kinase]; DCLRE1C [DNA cross-link repair 1C (P50 homolog, S. cerevisiae)]; DCN [decorin]; DCT [dopachrome tautomerase (dopachrome delta-isomerase, tyrosine-related protein 2)]; DCTN2 [dynactin 2 (p50)]; DDB1 [damage-specific DNA binding protein 1, 127 kDa]; DDB2 [damage-specific DNA binding protein 2, 48 kDa]; DDC [dopa decarboxylase (aromatic L-amino acid decarboxylase)]; DDIT3 [DNA-damage-inducible transcript 3]; DDRI [disoecdin domain receptor tyrosine kinase 1]; DDXX1 [DEAD (Asp-Glu-Ala-Asp) box polypeptide 1]; DDXX41 [DEAD (Asp-Glu-Ala-Asp) box polypeptide 41]; DDXX42 [DEAD (Asp-Glu-Ala-Asp) box polypeptide 42]; DDXX58 [DEAD (Asp-Glu-Ala-Asp) box polypeptide 58]; DEFA1 [defensin, alpha 1]; DEFAS [defensin, alpha 5, Paneth cell-specific]; DEFA6 [defensin, alpha 6, Paneth cell-specific]; DEFB1 [defensin, beta 1]; DEBF103B [defensin, beta 103B]; DEBF104A [defensin, beta 104A]; DEFB4A [defensin, beta 4A]; DEK [DEK oncoprotein, DENND1B [DENN/MADD domain containing 1B]; DES [desmin]; DGAT1 [diacylglycerol O-acetyltransferase homolog 1 (mouse)]; DGCR14 [DiGeorge syndrome critical region gene 14]; DGCR2 [DiGeorge syndrome critical region gene 2]; DGCR6 [DiGeorge syndrome critical region gene 6]; DGCR8L [DiGeorge syndrome critical region gene 6-like]; DGCR8 [DiGeorge syndrome critical region gene 8]; DGUK [deoxyuridine kinase]; DHFR [dihydrofolate reductase]; DHODH [dihydroorotate dehydrogenase]; DHDPS [dihydroxybutyrate synthase]; DHR57B [dehydrogenase/reductase (SDR family) member 7B]; DHR97 [dehydrogenase/reductase (SDR family) member 9]; DIAPH1 [diaphanous homolog 1 (Drosophila)]; Dicer1 [dicer 1, ribonuclease type III]; DIO2 [deiodinase, iodothyronine, type II]; DKK1 [dickkopf homolog 1 (Xenopus laevis)]; DLA1 [dihydroxypropionate S-acetyltransferase]; DLG2 [discs, large homolog 2 (Drosophila)]; DLG3 [disclike, large homolog 3 (Drosophila)]; DMAT1 [deleted in malignant brain tumors 1]; DMC1 [DMC1 dosage suppressor of mck1 homolog, meiosis-specific homologous recombination (yeast)]; DMD [dystrophin]; DMP1 [dentin matrix acidic phosphoprotein 1]; DMPK [dystrophia myotonica-protein kinase]; DMRT1 [doublesex and mab-3 related transcription factor 1]; DMXI2 [Dnax-like 2]; DNA2 [DNA replication helicase 2 homolog (yeast)]; DNAH11 [dynein, axonemal, heavy chain 1]; DNAH12 [dynein, axonemal, heavy chain 2]; DNAI1 [dynein, axonemal, intermediate chain 1]; DNAI2 [dynein, axonemal, intermediate chain 2]; DNAS11 [deoxyribonuclease I]; DNM2 [dynamin 2]; DNM3 [dynamin 3]; DNM1 [DNA (cytosine-5-) methyltransferase 1]; DNM3B [DNA (cytosine-5-) methyltransferase 3 beta]; DNTT [deoxyuridylate dehydrogenase, terminal]; DOCK1 [dedicator of cytokinesis 1]; DOCK3 [dedicator of cytokinesis 3]; DOCK8 [dedicator of cytokinesis 8]; DOK1 [docking protein 1, 62 kDa (downstream of tyrosine kinase 1)]; DOKL [dolichol kinase]; DPA1 [dolichyl-phosphate (UDP-N-acetylgalactosamine) N-acetylgalactosaminyltransferase 1 (GlcnAc-1-P transferase)]; DPEP1 [dipeptidase 1 (renal)]; DPH1 [diphosphatase homolog (S. cerevisiae)]; DPM1 [dolichyl-phosphate mannosyltransferase polypeptide 1, catalytic subunit]; DPP10 [dipeptidyl-peptidase 10]; DPP4 [dipeptidyl-peptidase 4]; DPYD [dihydropyrimidine dehydrogenase]; DRD2 [dopamine receptor D2]; DRD3 [dopamine receptor D3]; DRD4 [dopamine receptor D4]; DSC2 [desmocollin 2]; DSG1 [desmoglein 1]; DSG2 [desmoglein 2]; DSG3 [desmoglein 3 (pemphigus vulgaris antigen)]; DSP [desmopakin]; DTNA [dystrophia, alpha]; DTYMK [deoxythymidylate kinase (thymidylate kinase)]; DUOX1 [dual oxidase 1]; DUOX2 [dual oxidase 2]; DUSP1 [dual specificity phosphatase 1]; DUSP14 [dual specificity phosphatase 14]; DUSP2 [dual specificity phosphatase 2]; DUSP5 [dual specificity phosphatase 5]; DUT [deoxyuridinyltransferase]; DVL1 [detailed, dsh homolog 1 (Drosophila)]; DYN1C1 [dynein, cytoplasmic 2, heavy chain 1]; DYNLI1 [dynein, light chain, LC8-type 1]; DYSK1A [dual specificity tyrosine-(Y)-phosphorylation regulated kinase 1A]; DYSF [dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)]; E2F1 [E2F transcription factor 1]; EBF2 [early B-cell factor 2]; EBF3 [Epstein-Barr virus induced 3]; ECE1 [endothelin converting enzyme 1]; ECM1 [extracellular matrix protein 1]; EDA [ectodysplasin A]; EDAR [ectodysplasin A receptor]; EDN1 [endothelin 1]; EDNRA [endothelin receptor type A]; EDNRB [endothelin receptor type B]; EEF1A1 [eukaryotic translation elongation factor 1 alpha 1]; EEF1A2 [eukaryotic translation elongation factor 1 alpha 2]; EFEMP2 [EGF-containing fibulin-like extracellular matrix protein 2]; EFNA1 [ephrin-A1]; EFNB2 [ephrin-B2]; EFS [embryonal Fyn-associated substrate]; EGF [epidermal growth factor (beta-urogastrone)]; EGFIR [epidermal growth factor receptor (erythroleukemia viral (s-erb-b) oncogene homolog, avian)]; EGFR [early growth response 1]; EGR2 [early growth response 2]; EIF2F [etosynol homolog factor]; EHMT2 [spermatogenesis histone-lysine N-methyltransferase 2]; EIF2AK2 [eukaryotic translation initiation factor 2-alpha kinase 2]; EIF2S1 [eukaryotic translation initiation factor 2, subunit 1 alpha, 35 kDa]; EIF2S2 [eukaryotic translation initiation factor 2, subunit 2 beta, 38 kDa]; EIF3A [eukaryotic translation initiation factor 3, subunit A]; EIF4B [eukaryotic translation initiation factor 4B]; EIF4E [eukaryotic translation initiation factor 4E]; EIF4EBP1 [eukaryotic translation initiation factor 4E binding protein 1]; EIF4G1 [eukaryotic translation initiation factor 4 gamma, 1]; EIF6 [eukaryotic translation initiation factor 6]; ELAC2 [ehC homolog 2 (E. coli)]; ELANE [elastase, neutrophil expressed]; ELAV1 [ELAV (embryonic lethal, abnormal vision, Drosophila)-like 1 (Hu antigen R)]; ELF3 [E74-like factor 3 (ets domain transcription factor, epithelial-specific)]; ELF5 [E74-like factor 5 (ets domain transcription factor)]; ELM [elastin]; ELOVL4 [elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 4]; EMD [emerin]; EMILIN1 [elastin microfibril interfacer 1]; EMR2 [egf-like module containing, mucin-like, hormone receptor-like 2]; EN2 [enrolled homeobox 2]; ENG [endoglin]; ENO1 [enolase 1, (alpha)]; ENO2 [enolase 2 (gamma, neuronal)]; ENO3 [enolase 3 (beta, muscle)]; ENPP2 [ectonucleotide pyrophosphatase/phosphodiesterase 2]; ENPP3 [ectonucleotide pyrophosphatase/phosphodiesterase 3]; ENTPD1 [ectonucleotide triphosphatase diphosphohydrolase 1]; EP300 [E1A binding protein p300]; EPAS1 [endothelial PAS domain protein 1]; EPB42 [erythrocyte membrane protein band 4.2]; EPACAM [epithelial cell adhesion molecule]; EPHA1 [EPH receptor A1]; EPHIA2 [EPH receptor A2]; EPHIB2 [EPH receptor B2];
EPHB4 [EPH receptor B4]; EPHB6 [EPH receptor B6]; EPHPX1 [epoxide hydrolase 1, microsomal (xenobiotic)]; EPHX2 [epoxide hydrolase 2, cytoplasmic]; EPO [erythropoietin]; EPR5 [glutamyl-prolyl-tRNA synthetase]; EPX [eosinophil peroxidase]; ERBB2 [v-erb-b2 erythroblastoid leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)]; ERBB2IP [erb2 interacting protein]; ERBB3 [v-erb-b2 erythroblastoid leukemia viral oncogene homolog 3 (avian)]; ERBB4 [v-erb-a erythroblastoid leukemia viral oncogene homolog 4 (avian)]; ERCC1 [excision repair cross-complementing rodent repair deficiency, complementation group 1 (includes overlapping antisense sequence)]; ERCC2 [excision repair cross-complementing rodent repair deficiency, complementation group 2]; ERCC3 [excision repair cross-complementing rodent repair deficiency, complementation group 3 (xeroderma pigmentosum group B complementing)]; ERCC4 [excision repair cross-complementing rodent repair deficiency, complementation group 4]; ERCC5 [excision repair cross-complementing rodent repair deficiency, complementation group 5]; ERCC6 [excision repair cross-complementing rodent repair deficiency, complementation group 6]; ERCC6L [excision repair cross-complementing rodent repair deficiency, complementation group 6-like]; ERCC8 [excision repair cross-complementing rodent repair deficiency, complementation group 8]; ERO1L [ER01-like beta (S. cerevisiae)]; ERVK6 [endogenous retroviral sequence K, 6]; ERWVE1 [endogenous retroviral family W, env(C7), member 1]; ESR1 [estrogen receptor 1]; ESR2 [estrogen receptor 2 (ER beta)]; ESRRA [estrogen-related receptor alpha]; ESRRB [estrogen-related receptor beta]; ETS1 [v-ets erythroblastosis virus E26 oncogene homolog 1 (avian)]; ETS2 [v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)]; EWSR1 [Ewing sarcoma breakpoint region 1]; EY01 [exonuclease 1]; EYA1 [eyes absent homolog 1 (Drosophila)]; EZH2 [enhancer of zeste homolog 2 (Drosophila)]; EZR [ezrin]; FL0 [coagulation factor X]; FL1 [coagulation factor XI]; FL2 [coagulation factor XII (Hageman factor)]; FL3A [coagulation factor XIII, A1 polypeptide]; FL3B [coagulation factor XIII, B polypeptide]; F2 [coagulation factor II (thrombin)]; F2R [coagulation factor II (thrombin) receptor]; F2RL1 [coagulation factor II (thrombin) receptor-like 1]; F2RL3 [coagulation factor II (thrombin) receptor-like 3]; F3 [coagulation factor III (thromboplastin, tissue factor)]; F5 [coagulation factor V (procoagulant, labile factor)]; F7 [coagulation factor VII (serum prothrombin conversion accelerator)]; F8 [coagulation factor VIII, procoagulant component]; F9 [coagulation factor IX]; FABP1 [fatty acid binding protein 1, liver]; FABP2 [fatty acid binding protein 2, intestinal]; FABP4 [fatty acid binding protein 4, adipocyte]; FADD [Fas (TNFRSF6)-associated via death domain]; FADS1 [fatty acid desaturase 1]; FADS2 [fatty acid desaturase 2]; FAF1 [Fas (TNFRSF6) associated factor]; FAH [fumarylacetoacetate hydrolase (fumarylacetoacetase)]; FAM189B [family with sequence similarity 189, member B]; FAM92B [family with sequence similarity 92, member B]; FANC [Fanconi anemia, complementation group A]; FANCB [Fanconi anemia, complementation group B]; FANC [Fanconi anemia, complementation group C]; FANC2 [Fanconi anemia, complementation group D1]; FANC3 [Fanconi anemia, complementation group D2]; FANCE [Fanconi anemia, complementation group E]; FANC [Fanconi anemia, complementation group F]; FANCG [Fanconi anemia, complementation group G]; FANC1 [Fanconi anemia, complementation group I]; FANCL [Fanconi anemia, complementation group J]; FANCM [Fanconi anemia, complementation group M]; FANK1 [fibronectin type III and ankryin repeat domains 1]; FAS [Fas (TNF receptor superfamily, member 6)]; FASLG [Fas ligand (TNF superfamily, member 6)]; FASN [fatty acid synthase]; FASTK [Fas-activated serine/threonine kinase]; FBNL5 [fibulin 5]; FB1N [fibulin 1]; FBP1 [fructose-1,6-bisphosphatase 1]; FBXO32 [F-box protein 32]; FBXW7 [F-box and WD repeat domain containing 7]; FCAR [Fc fragment of IgA, receptor for]; FCER1A [Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide]; FCER1G [Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide]; FCER2 [Fc fragment of IgE, low affinity II, receptor for (CD23)]; FCGR1A [Fc fragment of IgG, high affinity Ia, receptor (CD64)]; FCGR2A [Fc fragment of IgG, low affinity IIa, receptor (CD32)]; FCGR2B [Fc fragment of IgG, low affinity IIb, receptor (CD32)]; FCGR3A [Fc fragment of IgG, low affinity IIIa, receptor (CD16a)]; FCGR3B [Fc fragment of IgG, low affinity IIIb, receptor (CD16b)]; FCN2 [ficolin (collagen/fibrinogen domain containing lectin) 2 (hucolin)]; FCN3 [ficolin (collagen/fibrinogen domain containing 3) (Hakata antigen)]; FCRL3 [Fc receptor-like 3]; FCRL6 [Fc receptor-like-6]; FET1 [farnesyl-diphosphate farnesyltransferase 1]; FDP5 [farnesyl diphosphate synthase (farnesylpyrophosphate synthetase, dimethylallyltransferase, geranyl transferase)]; FXD1 [ferredoxin 1]; FEN1 [flap structure-specific endonuclease 1]; FERMT1 [fermitin family homolog 1 (Drosophila)]; FERMT3 [fermitin family homolog 3 (Drosophila)]; FES [feline sarcoma oncogene]; FFA2 [free fatty acid receptor 2]; FG2 [fibronogen alpha chain]; FGB [fibronogen beta chain]; FGF1 [fibroblast growth factor 1 (acidic)]; FGF2 [fibroblast growth factor 2 (basic)]; FGF5 [fibroblast growth factor 5]; FGF7 [fibroblast growth factor 7 (keratinocyte growth factor)]; FGF8 [fibroblast growth factor 8 (androgen-induced)]; FGFBP2 [fibroblast growth factor binding protein 2]; FGFRI [fibroblast growth factor receptor 1]; FGFRI1P [FGFRI oncogene partner]; FGFRI2 [fibroblast growth factor receptor 2]; FGFRI3 [fibroblast growth factor receptor 3]; FGFRI4 [fibroblast growth factor receptor 4]; FGG [fibronogen gamma chain]; FGR [Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog]; FHIT [fragile histidine triad gene]; FHL1 [four and a half LIM domains 1]; FHL2 [four and a half LIM domains 2]; FBIP [fibroblast growth factor (acidic) intracellular binding protein]; FIGF [v-s induced growth factor (vascular endothelial growth factor D)]; FKBP1A [FK506 binding protein 1A, 12 kDa]; FKBP4 [FK506 binding protein 4, 59 kDa]; FKRP5 [FK506 binding protein 5]; FLCN [folliculin]; FLG [filaggrin]; FLG2 [filaggrin family member 2]; FLNA [filamin A, alpha]; FLNB [filamin B, beta]; FLT1 [fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)]; FLT3 [fms-related tyrosine kinase 3]; FLT3LG [fms-related tyrosine kinase 3 ligand]; FLT4 [fms-related tyrosine kinase 4]; FNM1 [formin 1]; FMOD [fibromodulin]; FMR1 [fragile X mental retardation 1]; FNI [fibronectin 1]; FOLH1 [folate hydrolase (prostate-specific membrane antigen 1)]; FOLR1 [folate receptor 1 (adult)]; FOS [FBFI murine osteosarcoma viral oncogene homolog]; FOXL2 [forkhead box L2]; FOXN1 [forkhead box N1]; FOXN2 [forkhead box N2]; FOXO3 [forkhead box O3]; FOXP3 [forkhead box P3]; FPGS [folic acid synthase]; FPR1 [formyl peptide receptor 1]; FPR2 [formyl peptide receptor 2]; FRAS1 [fraser
syndrome 1]); FREM2 [FRAS1 related extracellular matrix protein 2]; FSCN1 [fascin homolog 1, actin-bundling protein (Strongylocentrotus purpuratus)]; FSHB [follicle-stimulating hormone, beta polypeptide]; FSHR [follicle-stimulating hormone receptor]; FST [follistatin]; FTCD [formiminotransferase cycloleucineaminase]; FTH1 [ferritin, heavy polypeptide 1]; FTL [ferritin, light polypeptide]; FURIN [furin (paired basic amino acid cleaving enzyme)]; FUT1 [fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, H blood group)]; FUT2 [fucosyltransferase 2 (secretor status included)]; FUT3 [fucosyltransferase 3 (galactoside 3(4)-L-fucosyltransferase, Lewis blood group)]; FUT4 [fucosyltransferase 4 (alpha 1,3 fucosyltransferase, myeloid-specific)]; FUT7 [fucosyltransferase 7 (alpha 1,3 fucosyltransferase)]; FUT8 [fucosyltransferase 8 (alpha 1,6 fucosyltransferase)]; FXN [frataxin]; FYN [FYN oncogene related to SRC, FGR, YES]; FZD4 [frizzled homolog 4 (Drosophila)]; G6PC3 [glucose 6-phosphatase, catalytic]; G6PD [glucose-6-phosphate dehydrogenase]; GAA [glucosidase, alpha-1]; GAB2 [GRB2-associated binding protein 2]; GABB1 [gamma-aminobutyric acid (GABA) A receptor, beta 3]; GABRE [gamma-aminobutyric acid (GABA) A receptor, epsilon]; GAD1 [glutamate decarboxylase 1 (brain, 67 kDa)]; GAD2 [glutamate decarboxylase 2 (pancreatic islets and brain, 65 kDa)]; GADD45A [growth arrest and DNA-damage-inducible, alpha]; GAL [galanin prepropeptide]; GALK1 [galactokinase 1]; GALR1 [galanin receptor 1]; GAP43 [growth associated protein 43]; GAPDH [glyceraldehyde-3-phosphate dehydrogenase]; GART [phosphoribosylpyrophosphate formyltransferase, phosphoribosylpyrophosphate synthetase, phosphoribosylaminomimidazole synthetase]; GAST [gas]; GATA1 [GATA binding protein 1 (global transcription factor 1)]; GATA2 [GATA binding protein 2]; GATA3 [GATA binding protein 3]; GATA4 [GATA binding protein 4]; GATA6 [GATA binding protein 6]; GBA [glucosidase, beta, acid]; GBAB [glucosidase, beta, acid 3 (cytosolic)]; GBE1 [glucan 1-4-beta, branching enzyme 1]; GC [group-specific component (vitamin D binding protein)]; GCC [glucagon]; GCH1 [GTP cyclohydrolase I]; GCKR [glucokinase (hexokinase 4) regulator]; GCLC [glutamate-cysteine ligase, catalytic subunit]; GCLM [glutamate-cysteine ligase, modifier subunit]; GCNT2 [N-acetylglucosaminyl (N-acetyl) transferase 2, 1-branched enzyme (1 blood group)]; GDAP1 [ganglioside-induced differentiation-associated protein 1]; GFAP [growth differentiation factor 15]; GDNF [glial cell derived neurotrophic factor]; GFAP [glial fibrillary acidic protein]; GGH [gamma-glutamyl hydrolase (conjugase, folypolygamma-mutaglutamyl hydrolase)]; GGT1 [gamma-glutamyltransferase 1]; GGT2 [gamma-glutamyltransferase 2]; GH1 [growth hormone 1]; GHHR [growth hormone receptor]; GHRH [growth hormone releasing hormone]; GHRH [growth hormone releasing hormone]; GHRH [growth hormone releasing hormone]; GHRH [growth hormone secretagogue receptor]; GIF [gastric intrinsic factor (vitamin B synthesis)]; GIP [gastric inhibitory polypeptide]; GJA1 [gap junction protein, alpha 1, 43 kDa]; GJA4 [gap junction protein, alpha 4, 37 kDa]; GJB2 [gap junction protein, beta 2, 26 kDa]; GLA [galactosidase, alpha]; GLB1 [galactosidase, beta 1]; GLI2 [GLI family zinc finger 2]; GLMN [glomulin, FKBP38 associated protein]; GLRT2 [glutaredoxin (thioltransferase)]; GLS [glutaminase]; GLT2D1 [glyclosyltransferase 25 domain containing 1]; GLUL [glutamate-ammonia ligase (glutamine synthetase)]; GLYAT [glycine-N-acyltransferase]; GM2A [GM2 ganglioside activator]; GMDS [GDP-mannose 4,6-dehydratase]; GNA12 [guanine nucleotide binding protein (G protein) alpha 12]; GNA13 [guanine nucleotide binding protein (G protein), alpha 13]; GNA11 [guanine nucleotide binding protein (G protein), alpha inhibiting activity polypeptide 1]; GNAQ [guanine nucleotide binding protein (G protein), alpha activating activity polypeptide 0]; GNAT2 [guanine nucleotide binding protein (G protein), gamma 2]; GNLY [granulysin]; GNPAT [glycerocephosphate O-acetyltransferase]; GNPD2 [glycerocephosphate-6-phosphate deaminase 2]; GNRH1 [gonadotropin-releasing hormone 1 (luteinizing-releasing hormone)]; GNRHR [gonadotropin-releasing hormone receptor]; GOLGA8B [golgin A8 family, member B]; GOLGB1 [golgin B1]; GOT1 [glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)]; GOT2 [glutamic-oxaloacetic transaminase 2, mitochondrial (aspartate aminotransferase 2)]; GP1 [glycoprotein Ib, platelet, alpha polypeptide]; GP2 [glycoprotein 2 (zymogen granule membrane)]; GP6 [glycoprotein V, platelet]; GPBAR1 [G protein-coupled bile acid receptor 1]; GPC3 [glypican 5]; GPP [glyceraldehyde-3-phosphate isomerase]; GPLD1 [glycosylphosphatidylinositol specific phospholipase D1]; GPNI [GPN-locus G/F pseudo]; GPR1 [G protein-coupled receptor 1]; GPR12 [G protein-coupled receptor 12]; GPR123 [G protein-coupled receptor 123]; GPR143 [G protein-coupled receptor 143]; GPR15 [G protein-coupled receptor 15]; GPR182 [G protein-coupled receptor 182]; GPR44 [G protein-coupled receptor 44]; GPR77 [G protein-coupled receptor 77]; GPRAS1 [G protein-coupled receptor associated sorting protein 1]; GPRC6A [G protein-coupled receptor, family C, group 6, member A]; GPT [glutamic-pyruvic transaminase (alanine aminotransferase)]; GPX1 [glutathione peroxidase 1]; GPX2 [glutathione peroxidase 2 (gastrointestinal)]; GPX3 [glutathione peroxidase 3 (plasma)]; GRAP2 [GRB2-related adaptor protein 2]; GRB2 [growth factor receptor-bound protein 2]; GRIK2 [glutamate receptor, ionotropic, AMPA 2]; GRIK1 [glutamate receptor, ionotropic, N-methyl D-aspartate 1]; GRIK2A [glutamate receptor, ionotropic, N-methyl-D-aspartate 2A]; GRIK2B [glutamate receptor, ionotropic, N-methyl-D-aspartate 2B]; GRIK2C [glutamate receptor, ionotropic, N-methyl-D-aspartate 20]; GRIK2D [glutamate receptor, ionotropic, N-methyl-D-aspartate 2D]; GRIK3A [glutamate receptor, ionotropic, N-methyl-D-aspartate 3A]; GRIK3B [glutamate receptor, ionotropic, N-methyl-D-aspartate 3B]; GRIK5 [G protein-coupled receptor kinase 5]; GRLF1 [glucocorticoid receptor DNA binding factor 1]; GRLM1 [glutamate receptor, metabotropic 1]; GRP [gastrin-releasing peptide]; GRPR [gastrin-releasing peptide receptor]; GSC [gосеоsidе homebox]; GSC2 [gосеоsidе homebox 2]; GSDMB [gосеоsidе B]; GSK3B [gосеоsidе synthase kinase 3 beta]; GSN [gосеоsin]; GSR [glutathione reductase]; GSS [glutathione synthetase]; GSTA1 [glutathione S-transferase alpha 1]; GSTA2 [glutathione S-transferase alpha 2]; GSTM1
[glutathione S-transferase mu 1]; GSTM3 [glutathione S-transferase mu 3 (brain)]; GSTT2 [glutathione S-transferase omega 2]; GSTT1 [glutathione S-transferase theta 1]; GT2FA1 [general transcription factor IIA, 1, 19/37 kDa]; GT2FB1 [general transcription factor IIF, polypeptide 1, 1, 44 kDa]; GT2FH1 [general transcription factor I1H, polypeptide 1, 44 kDa]; GT2FH2 [general transcription factor I1H, polypeptide 4, 52 kDa]; GT2FH5 [general transcription factor I1H, polypeptide 5]; GT2F2 [general transcription factor II]; GT2FA3 [general transcription factor IIIA]; GUC4 [guanylate cyclase activator 2A (guanylin)]; GUC5B [guanylate cyclase activator 2B (uroguanylin)]; GUCY2C [guanylate cyclase 2C (heat stable enterotoxin receptor)]; GUK [guanylate kinase 1]; GULP1 [GULP, engulfment adaptor PTB domain containing 1]; GUSB [glucuronidase, beta]; GYPA [glycoprotein A (MN blood group)]; GYPB [glycoprotein B (MN blood group)]; GYPC [glycoprotein C (Gerbich blood group)]; GYPE [glycoprotein E (MN blood group)]; GYS1 [glycogen synthase 1 (muscle)]; GZMA [granulysin (granulysin 1, cytotoxic T-lymphocyte-associated serine esterase 3)]; GZMB [granulysin B (granulysin 2, cytotoxic T-lymphocyte-associated serine esterase 1)]; GZMK [granulysin K (granulysin 3, tryptase II)]; H1F0 [H1 histone family, member 0]; H2AFX [H2A histone family, member X]; HAPB2 [hyaluronic binding protein 2]; HACL1 [2-[2-hydroxyethyl]-CoA lyase 1]; HADH [hydroxacyl-Coenzyme A dehydrogenase 3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit]; HAL [histidine ammonia-lyase]; HAMP [hepcidin antimicrobial peptide]; HAPLN1 [hyaluronic and proteoglycan link protein 1]; HAVCR1 [hepatitis A virus cellular receptor 1]; HAVCR2 [hepatitis A virus cellular receptor 2]; HAX1 [HECLS1 associated protein X-1]; HBA1 [hemoglobin, alpha 1]; HBA2 [hemoglobin, alpha 2]; HBH [hemoglobin, beta]; HBE1 [hemoglobin, epsilon 1]; HBEFG [heparin-binding EGF-like growth factor]; HBGG [hemoglobin, gamma G]; HCCS [holocarboxylase synthase (coenzyme A-heme); HCK [hemopoietic cell kinase]; HCRTR1 [hypocretin (orexin) receptor precursor]; HCRTR1 [hypocretin (orexin) receptor precursor]; HCRTR2 [hypocretin (orexin) receptor 2]; HEST [hematopoietic cell signal transducer]; HDAC1 [histone deacetylase 1]; HDAC2 [histone deacetylase 2]; HDAC6 [histone deacetylase 6]; HDAC9 [histone deacetylase 9]; HDC [histidine decarboxylase]; HERC2 [hect domain and RLD 2]; HES1 [hairst and enhancer of split 1, Rosposhila]; HES6 [hairst and enhancer of split 6, Rosposhila]; HESX1 [HESX] homeobox 1]; HFXA [hexosaminidase A (alpha polypeptide)]; HFXB [hexosaminidase B (beta polypeptide)]; HFE [hemochromatosis]; HGF [hepatocty growth factor (hepatopoietin A; scatter factor)]; HGS [hepatocty growth factor regulated tyrosine kinase substrate]; HGSNAT [heparan-alpha-glucosaminide N-acetyltransferase]; HIF1A [hypoxya inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)]; HIFNE1 [hypoxya inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)]; HINT1 [histidine triad nucleotide binding protein 1]; HIPK2 [homeodomain interacting protein kinase 2]; HIRA [HIR histone cell cycle regulation defective homolog A (S. cerevisiae)]; HIST1H1B [histone cluster 1, H3b]; HIST1H3E [histone cluster 1, H3e]; HIST2H2AC [histone cluster 2, H2ac]; HIST2H3C [histone cluster 2, H3c]; HIST4H4 [histone cluster 4, H4]; HJURP [Holliday junction recognition protein]; HK2 [hexokinase 2]; HLA-A [major histocompatibility complex, class I, A]; HLA-B [major histocompatibility complex, class I, B]; HLA-C [major histocompatibility complex, class I, C]; HLA-DM [major histocompatibility complex, class II, DM alpha]; HLA-DMB [major histocompatibility complex, class II, DM beta]; HLA-DOA [major histocompatibility complex, class II, DO alpha]; HLA-DOB [major histocompatibility complex, class II, DO beta]; HLA-DR1 [major histocompatibility complex, class II, DR alpha]; HLA-DRB1 [major histocompatibility complex, class II, DR beta]; HLA-DRB3 [major histocompatibility complex, class II, DR beta 3]; HLA-DRB4 [major histocompatibility complex, class II, DR beta 4]; HLA-DRB5 [major histocompatibility complex, class II, DR beta 5]; HLA-E [major histocompatibility complex, class I, E]; HLA-F [major histocompatibility complex, class I, F]; HLA-G [major histocompatibility complex, class I, G]; HLA-H [major histocompatibility complex, class I, H]; HLA-J [major histocompatibility complex, class I, J]; HLA-K [major histocompatibility complex, class I, K]; HLA-L [major histocompatibility complex, class I, L]; HLA-M [major histocompatibility complex, class I, M]; HLA-N [major histocompatibility complex, class I, N]; HLA-O [major histocompatibility complex, class I, O]; HLA-P [major histocompatibility complex, class I, P]; HLA-Q [major histocompatibility complex, class I, Q]; HLA-R [major histocompatibility complex, class I, R]; HLA-S [major histocompatibility complex, class I, S]; HLA-T [major histocompatibility complex, class I, T]
ytriptamine (serotonin) receptor 1A; HTR2A [5-hydroxytriptamine (serotonin) receptor 2A]; HTR3A [5-hydroxytriptamine (serotonin) receptor 3A]; HTRA1 [HTRA serine peptidase 1]; HTT [huntingtin]; HUS1 [HUS1 checkpoint homolog (S. pombe)]; HUWE1 [HECT, UBA and WWE domain containing 1]; HYAL1 [hyaluronoglucosaminidase 1]; HYLS1 [hydroxethyladipate syndrome 1]; IAPP [islet amyloid polypeptide]; IBSP [integrin-binding sialoprotein]; ICAM1 [intercellular adhesion molecule 1]; ICAM2 [intercellular adhesion molecule 2]; ICAM3 [intercellular adhesion molecule 3]; ICAM4 [intercellular adhesion molecule 4 (Landsteiner-Wiener blood group)]; ICOS [inducible T-cell co-stimulator]; ICOSLG [inducible T-cell co-stimulator ligand]; ID1 [inhibitor of DNA binding 1, dominant negative helix-loop-helix protein]; ID2 [inhibitor of DNA binding 2, dominant negative helix-loop-helix protein]; IDO1 [indoleamine 2-3-dioxygenase 1]; IDS [iduronate 2-sulfatase]; IDUA [iduronidase, alpha-L-1]; IF127 [interferon, alpha-inducible protein 27]; IFI50 [interferon, gamma-inducible protein 30]; IFITM1 [interferon induced transmembrane protein 1 (9-27)]; IFNA1 [interferon, alpha 1]; IFNA2 [interferon, alpha 2]; IFNAR1 [interferon (alpha, beta and omega) receptor 1]; IFNAR2 [interferon (alpha, beta and omega) receptor 2]; IFNB1 [interferon, beta 1, fibroblast]; IFNG [interferon, gamma]; IFNGR1 [interferon gamma receptor 1]; IFNGR2 [interferon gamma receptor 2 (interferon gamma transducer 1)]; IGF1 [insulin-like growth factor 1 (somatomedin C)]; IGF1R [insulin-like growth factor 1 receptor]; IGF2 [insulin-like growth factor 2 (somatomedin A)]; IGF2R [insulin-like growth factor 2 receptor]; IGFBP1 [insulin-like growth factor binding protein 1]; IGFBP2 [insulin-like growth factor binding protein 2, 36.6 kDa]; IGFBP3 [insulin-like growth factor binding protein 3]; IGFBP4 [insulin-like growth factor binding protein 4]; IGFBP5 [insulin-like growth factor binding protein 5]; IGHA1 [immunoglobulin heavy constant alpha 1]; IGHE [immunoglobulin heavy constant epsilon]; IGHG1 [immunoglobulin heavy constant gamma 1 (Gm marker)]; IGHG3 [immunoglobulin heavy constant gamma 3 (Gm marker)]; IGHG4 [immunoglobulin heavy constant gamma 4 (Gm marker)]; IGHM [immunoglobulin heavy constant mu]; IGHMBP2 [immunoglobulin mu binding protein 2]; IGKC [immunoglobulin kappa constant]; IGKV2D-29 [immunoglobulin kappa variable 2D-29]; IGLL1 [immunoglobulin lambda-like polypeptide 1]; IGSF1 [immunoglobulin superfamily, member 1]; IKKBAP [inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein]; IKKBD [inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta]; IKKBE [inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon]; IKKCG [inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma]; IKZF1 [IKAROS family zinc finger 1 (IKAROS)]; IKZF2 [IKAROS family zinc finger 2 (Helios)]; IL10 [interleukin 10]; IL10RA [interleukin 10 receptor, alpha]; IL10RB [interleukin 10 receptor, beta]; IL11 [interleukin 11]; IL12A [interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)]; IL12B [interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)]; IL12RB1 [interleukin 12 receptor, beta 1]; IL12RB2 [interleukin 12 receptor, beta 2]; IL13 [interleukin 13]; IL13RA1 [interleukin 13 receptor, alpha 1]; IL13RA2 [interleukin 13 receptor, alpha 2]; IL15 [interleukin 15]; IL15RA [interleukin 15 receptor, alpha]; IL16 [interleukin 16 (lymphocyte chemoattractant factor)]; IL17A [interleukin 17A]; IL17F [interleukin 17F]; IL17RA [interleukin 17 receptor B]; IL17RC [interleukin 17 receptor C]; IL18 [interleukin 18 (interferon-gamma-inducing factor)]; IL18BP [interleukin 18 binding protein]; IL18R1 [interleukin 18 receptor 1]; IL18RAP [interleukin 18 receptor accessory protein]; IL19 [interleukin 19]; IL1A [interleukin 1, alpha]; IL1B [interleukin 1, beta]; IL1F9 [interleukin 1 family, member 9]; IL1R1 [interleukin 1 receptor, type I]; IL1RAP [interleukin 1 receptor accessory protein]; IL1R1 [interleukin 1 receptor-like 1]; URN [interleukin 1 receptor antagonist]; IL2 [interleukin 2]; IL20 [interleukin 20]; IL21 [interleukin 21]; IL21R [interleukin 21 receptor]; IL22 [interleukin 22]; IL23A [interleukin 23, alpha subunit p19]; IL23R [interleukin 23 receptor]; IL24 [interleukin 24]; IL25 [interleukin 25]; IL26 [interleukin 26]; IL27 [interleukin 27]; IL27RA [interleukin 27 receptor, alpha]; IL29 [interleukin 29 (interferon, lambda 1)]; IL2RA [interleukin 2 receptor, alpha]; IL2RB [interleukin 2 receptor, beta]; IL2RG [interleukin 2 receptor, gamma (severe combined immunodeficiency)]; IL3 [interleukin 3 (colony-stimulating factor, multiple)]; IL31 [interleukin 31]; IL32 [interleukin 32]; IL35 [interleukin 33]; IL3RA [interleukin 3 receptor, alpha (low affinity)]; IL4 [interleukin 4]; IL4R [interleukin 4 receptor]; IL5 [interleukin 5 (colony-stimulating factor, eosinophilic)]; IL5RA [interleukin 5 receptor, alpha]; IL6 [interleukin 6 (interferon, beta 2)]; IL6R [interleukin 6 receptor]; IL6ST [interleukin 6 signal transducer (gp130, oncostatin M receptor)]; IL7 [interleukin 7 receptor]; IL8 [interleukin 8]; IL9 [interleukin 9]; IL9R [interleukin 9 receptor]; ILK [integrin-linked kinase]; IMPS [intramembrane protease 5]; INCENP [inner centromere protein antigen 155/155 kDa]; ING1 [inhibitor of growth family, member 1]; INHA [inhibin, alpha]; INHBA [inhibin, beta A]; INPP4A [inositol polyphosphate-4-phosphatase, type 1, 107 kDa]; INPP5D [inositol polyphosphate-5-phosphatase, 145 kDa]; INPP5E [inositol polyphosphate-5-phosphatase, 72 kDa]; INPPPL1 [inositol polyphosphate phosphatase-like 1]; INS [insulin]; INS1L3 [insulin-like 3 (Lydig cell)]; INSR [insulin receptor]; IPO13 [importin 13]; IP07 [importin 7]; IQGAP1 [IQ motif containing GTPase activating protein 1]; IRAK1 [interleukin-1 receptor-associated kinase 1]; IRAK3 [interleukin-1 receptor-associated kinase 3]; IRAK4 [interleukin-1 receptor-associated kinase 4]; IRF1 [interleukin regulatory factor 1]; IRF2 [interleukin regulatory factor 2]; IRF3 [interleukin regulatory factor 3]; IRF4 [interleukin regulatory factor 4]; IRF5 [interleukin regulatory factor 5]; IRF7 [interleukin regulatory factor 7]; IRF8 [interleukin regulatory factor 8]; IRGM [immunity-related GTPase family, M]; IRS1 [insulin receptor substrate 1]; IRS2 [insulin receptor substrate 2]; IRS4 [insulin receptor substrate 4]; ISG15 [ISG15 ubiquitin-like modifier]; ITCH [itchy E3 ubiquitin protein ligase homolog (mouse)]; ITFG1 [integrin alpha FG-GAP repeat containing 1]; ITGA1 [integrin, alpha 1]; ITGA2 [integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)]; ITGA2B [integrin, alpha 2 (platelet glycoprotein IIb of IIa/IIIa complex, antigen CD41)]; ITGA3 [integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)]; ITGA4 [integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)]; ITGA5 [integrin, alpha 5 (fibronectin receptor, alpha polypeptide)]; ITGA6 [integrin, alpha 6]; ITGA8 [integrin, alpha 8]; ITGA9 [integrin, alpha 9 (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)]; ITGAI [integrin, alpha I (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)];
ITGAM [integrin, alpha M (complement component 3 receptor 3 subunit)]; ITGAV [integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)]; ITGAX [integrin, alpha X (complement component 3 receptor 4 subunit)]; ITGB1 [integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK1)]; ITGB2 [integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)]; ITGB3 [integrin, beta 3 (platelet glycoprotein IIla, antigen CD61)]; ITGB3BP [integrin beta 3 binding protein (beta3-endonexin)]; ITGB4 [integrin, beta 4]; ITGB6 [integrin, beta 6]; ITGB7 [integrin, beta 7]; ITIH4 [inter-alpha (globulin) inhibitor H4 (plasma Kallikrein-sensitive glycoprotein)]; ITK [IL-2-inducible T-cell kinase]; ITN1 [interlec- tin 1 (galactofuranose binding)]; ITNL2 [interleucin 2]; ITPA [inosine triphosphatase (nucleoside triphosphate pyrophosphatase)]; ITPR1 [inositol 1,4,5-triphosphate receptor, type 1]; ITPR3 [inositol 1,4,5-triphosphate receptor, type 3]; IVD [isovaleryl Coenzyme A dehydrogenase]; IVL [involutin]; IVNS1ABP [influenza virus NS1 binding protein]; JAG1 [jagged 1 (Aaligille syndrome)]; JAK1 [Janus kinase 1]; JAK2 [Janus kinase 2]; JAK3 [Janus kinase 3]; JAKMIP1 [Janus kinase and microtubule interacting protein 1]; JMD6 [jun monji domain containing 6]; JPH4 [uncharacterized]; JRKL [kerky homolog (mouse)]; JUN [jun oncogene]; JUND [jun D proto-oncogene]; JUP [junction plakoglobin]; KARS [lysyl-tRNA synthetase]; KAT5 [K (lysine) acetyltransferase 5]; KCNA2 [potassium voltage-gated channel subfamily G member 2]; KCNAD5 [potassium voltage-gated channel, shaker-related subfamily, member 2]; KCND1 [potassium voltage-gated channel, shaker-related subfamily, member 5]; KCND1 [potassium voltage-gated channel, shal-related subfamily member 1]; KCNH2 [potassium voltage-gated channel, subfamily H (egulated), member 2]; KCNIP4 [Kv channel interacting protein 4]; KCNMA1 [potassium large conductance calcium-activated channel, subfamily M, alpha member 1]; KCNMB1 [potassium large conductance calcium-activated channel, subfamily M, beta member 1]; KCNNS3 [potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3]; KLK1 [kalikrein 1]; KLK11 [kalikrein-related peptidase 11]; KLK13 [kalikrein-related peptidase 3]; KLKB1 [kalikrein B, plasma (Fletcher factor) c]; KLRB1 [killer cell lectin-like receptor subfamily B, member 1]; KLRD1 [killer cell lectin-like receptor subfamily C, member 1]; KLRD1 [killer cell lectin-like receptor subfamily D, member 1]; KLRK1 [killer cell lectin-like receptor subfamily K, member 1]; KNG1 [kiningen 1]; KPNA1 [karyopherin alpha 1 (importin alpha 5)]; KPNA2 [karyopherin alpha 2 (RAG cohort 1, importin alpha 1)]; KPNB1 [karyopherin (importin) beta 1]; KRAS [v-Ki-ras Kirsten rat sarcoma viral oncogene homolog]; KRT1 [keratin 1]; KRT10 [keratin 10]; KRT13 [keratin 13]; KRT14 [keratin 14]; KRT16 [keratin 16]; KRT18 [keratin 18]; KRT19 [keratin 19]; KRT20 [keratin 20]; KRT5 [keratin 5]; KRT7 [keratin 7]; KRT8 [keratin 8]; KRT9 [keratin 9]; KRTAP19-3 [keratin associated protein 19-3]; KRTAP2-1, keratin associated protein 2-1]; L1CAM [L1 cell adhesion molecule]; LACTB [lactamase, beta]; LAG3 [lymphocyte activation gene 3]; LALBA [lactalbumin, alpha-1]; LAMA1 [laminin alpha 1]; LAMA2 [laminin alpha 2]; LAMA3 [laminin alpha 3]; LAMA4 [laminin alpha 4]; LAMB1 [laminin beta 1]; LAMB2 [laminin beta 2 (laminin 5)]; LAMB3 [laminin beta 3]; LAMC1 [laminin, gamma 1 (formerly LAMB2)]; LAMC2 [laminin, gamma 2]; LAP1 [lysosomal-associated membrane protein 1]; LAP2 [lysosomal-associated membrane protein 2]; LAP3 [lysosomal-associated membrane protein 3]; LAP3 [lysosome-associated protein 3]; LAP4 [lysosome-associated protein 3]; LAPT4A [lysosomal protein transport membrane 4 alpha]; LAT [linker for activation of T cells]; LBP [lipopolysaccharide binding protein]; LBR [lamin B receptor]; LBCORL1 [lbcorl homolog (mouse)]; LCAT [lecithin-cholesterol acyltransferase]; LCK [lymphocyte-specific protein tyrosine kinase]; LCN1 [lipocalin 1 (tau pralubin)]; LCN2 [lipocalin 2]; LCP1 [lymphocyte cyto- solic protein 1 (L-plastin)]; LCT [lactase]; LDLR [low density lipoprotein receptor]; LDLRAP1 [low density lipoprotein receptor adaptor protein 1]; LECT2 [leukocyte cell-derived chemotaxin 2]; LELP1 [late cornified envelope-like proline-rich 1]; LEMD3 [lem domain containing 3]; LEP [leptin]; LEPR [leptin receptor]; LGALS1 [lectin, galecto- side-binding, soluble, 1]; LGALS3 [lectin, galectoside-binding, soluble, 3]; LGALS3BP [lectin, galectoside-binding, soluble, 3 binding protein]; LGALS4 [lectin, galectoside-binding, soluble, 4]; LGALS9 [lectin, galectoside-binding, soluble, 9]; LGAL9B [lectin, galectoside-binding, soluble, 9B]; LGGR4 [leucine-rich repeat-containing G protein-coupled receptor 4]; LHCGR [luteinizing hormone/chorio- gonadotropin receptor]; LIF [leukemia inhibitory factor (cholinergic differentiation factor)]; LIFR [leukemia inhibitory factor receptor alpha]; LIIG1 [ligase I, DNA, ATP-dependent]; LIIG3 [ligase III, DNA, ATP-dependent]; LIIG4 [ligase IV, DNA, ATP-dependent]; LIILRA3 [leukocyte immunoglobulin-like receptor, subfamily A (without TM domain), member 3]; LIILRB4 [leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 4]; LIMS1 [LIM and senescent cell antigen-like domains 1]; LIPA [lipase A, lysosomal acid, cholesterol esterase]; LIPC [lipase, hepatic]; LIPE [lipase, hormone-sensitive]; LIPG [lipase, endothelial]; LMAN1 [lectin, mannose-binding, 1]; LMAN2 [leishmanolysin-like (metalloproteinase M8 family)]; LMNA [lamin N]; LMNB1 [lamin B1]; LMNB2 [lamin B2]; LOC646627 [phospholipase inhibitor]; LOX [lysyl oxi-
1, cyclin H assembly factor (Xenopus laevis)); MOG [myelin oligodendrocyte glycoprotein]; MOGS [mannosyl-oligosaccharide glucosidase]; MPG [N-methylpurine-DNA glycosylase]; MPL [myeloproliferative leukemia virus oncogene]; MPO [myeloperoxidase]; MPZ [myelin protein zero]; MR1 [major histocompatibility complex, class I-related]; MRCA1 [mannose receptor, C type 1]; MRCA2 [mannose receptor, C type 2]; MRCE1 [mannose receptor, C type 2]; MRCE1A [MRE11 meiotic recombination 11 homolog A (S. cerevisiae)]; MRGPRX1 [MAS-related GPR, member X1]; MRPL28 [mitochondrial ribosomal protein L28]; MRPL40 [mitochondrial ribosomal protein L40]; MRPS16 [mitochondrial ribosomal protein S16]; MRPS22 [mitochondrial ribosomal protein S22]; MS4A1 [membrane-spanning 4-domains, subfamily A, member 1]; MS4A2 [membrane-spanning 4-domains, subfamily A, member 2 (Fc fragment of IgE, high affinity I, receptor for; beta polypeptide)]; MS4A3 [membrane-spanning 4-domains, subfamily A, member 3 (hematopoietic cell-specific)]; MS2H [mitS homolog 2, colon cancer, nonpolyposis type 1 (E. coli)]; MS5H [mitS homolog 5 (E. coli)]; MSH6 [mitS homolog 6 (E. coli)]; MSLN [mesothelin]; MSN [mosesin]; MSR1 [macrophage scavenger receptor family]; MST1 [macrophage stimulating 1 (hepatocyte growth factor-like)]; MST1R [macrophage stimulating 1 receptor (c-met-related tyrosine kinase)]; MSTD [myostatin]; MSX2 [msh homebox 2]; MT2A [metallothionein 2A]; MTC2 [mitochondrial carrier homolog 2 (C. elegans)]; MTO2 [mitochondrially encoded cytochrome c oxidase II]; MTPCP1 [mature T-cell proliferation 1]; MT-CDY [mitochondrially encoded cytochrome b]; MTHFD1 [methylene-tetrahydrofolate dehydrogenase (NADP+)-dependent 1, methenyl-tetrahydrofolate cyclodehydrase, formyl-tetrahydrofolate synthetase]; MTHFR [5’-10’-methylene-tetrahydrofolate reductase (NADPH)]; MTHMR1 [myotubularin related protein 14]; MTMR2 [myotubularin related protein 2]; MT-ND1 [mitochondrially encoded NADH dehydrogenase 1]; MT-ND2 [mitochondrially encoded NADH dehydrogenase 2]; MTO2 [mechanistic target of rapamycin (serine/threonine kinase)]; MTR [5’-methylene-tetrahydrofolate-homocysteine methyltransferase]; MTRR [5’-methylene-tetrahydrofolate-homocysteine methyltransferase reductase]; MTTLP [microsomal triglyceride transfer protein]; MTX1 [metaxin 1]; MUC1 [mucin 1, cell surface associated]; MUC12 [mucin 12, cell surface associated]; MUC16 [mucin 16, cell surface associated]; MUC19 [mucin 19, oligomeric]; MUC2 [mucin 2, oligomeric mucin/gel-forming]; MUC3A [mucin 3A, cell surface associated]; MUC3B [mucin 3B, cell surface associated]; MUC4 [mucin 4, cell surface associated]; MUC5AC [mucin SAC, oligomeric mucin/gel-forming]; MUC5B [mucin 5B, oligomeric mucin/gel-forming]; MUC6 [mucin 6, oligomeric mucin/gel-forming]; MUC7 [mucin 7, secreted]; MUS81 [MUS81 endonuclease homolog (S. cerevisiae)]; MUSK [muscle, skeletal, receptor tyrosine kinase]; MUT [methylmalonyl Coenzyme A mutase]; MVK [mevalonate kinase]; MVP [major vault protein]; MX1 [myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)]; MYB [myb myeloblastosis viral oncogene homolog (avian)]; MYBPH [myosin binding protein II]; MYC [myc myelocytomatosis viral oncogene homolog (avian)]; MYCN [myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian)]; MYD88 [myeloid differentiation primary response gene (88)]; MYH1 [myosin, heavy chain 1, skeletal muscle, adult]; MYH10 [myosin, heavy chain 10, non-muscle]; MYH11 [myosin, heavy chain 11, smooth muscle]; MYH14 [myosin, heavy chain 14, non-muscle]; MYH2 [myosin, heavy chain 2, skeletal muscle, adult]; MYH3 [myosin, heavy chain 3, skeletal muscle, embryonic]; MYH6 [myosin, heavy chain 6, cardiomyocyte, alpha]; MYH7 [myosin, heavy chain 7, cardiomyocyte, beta]; MYH18 [myosin, heavy chain 8, skeletal muscle, perinatal]; MYH9 [myosin, heavy chain 9, non-muscle]; MYL2 [myosin, light chain 2, regulatory, cardiomyocyte, slow]; MYL3 [myosin, light chain 3, alkali, ventricular, skeletal, slow]; MYL7 [myosin, light chain 7, regulatory]; MYL9 [myosin, light chain 9, regulatory]; MYLK [myosin light chain kinase]; MYO15A [myosin XVIA]; MYO1A [myosin IA]; MYO1F [myosin IF]; MYO3A [myosin 11A]; MYO5A [myosin VA (heavy chain 12, myosin)]; MYO6 [myosin VI]; MYO7A [myosin VIIA]; MYO9B [myosin IXB]; MYOC [myocilin, trabecular meshwork inducible glucocorticoid response]; MYOD1 [myogenic differentiation 1]; MYOM2 [myomesin (M-protein) 2, 165 kDa]; MYST1 [MYST histone acetyltransferase 1]; MYST2 [MYST histone acetyltransferase 2]; MYST3 [MYST histone acetyltransferase (monocytic leukemia 3)]; MYST4 [MYST histone acetyltransferase (monocytic leukemia 4)]; NAGA [N-acetylglactosaminidase, alpha-]; NAGLU [N-acetylgalcosaminidase, alpha-]; NAMPT [nicotinamide phosphoribosyltransferase]; NANO1 [Nanog homeobox]; NANS1 [nanos homolog 1 (Drosophila)]; NAPA [N-ethylmaleimidesensitive factor attachment protein, alpha]; NAT1 [N-acetyltransferase 1 (arylamine N-acetyltransferase)]; NAT2 [N-acetyltransferase 2 (arylamine N-acetyltransferase)]; NAT9 [N-acetyltransferase 9 (GCSN-related, putative)]; NBSA [neurobeachin]; NBN [nibrin]; NCAM1 [neural cell adhesion molecule 1]; NCF1 [neutrophil cytosolic factor 1]; NCF2 [neutrophil cytosolic factor 2]; NCF4 [neutrophil cytosolic factor 4, 40 kDa]; NCK1 [NCK adaptor protein 1]; NCL [nucleolus]; NCOA1 [nuclear receptor coactivator 1]; NCOA2 [nuclear receptor coactivator 2]; NCOA1 [nuclear receptor co-repressor]; NCR3 [natural cytotoxicity triggering receptor 3]; NDUF13 [NADH dehydrogenase (ubiquinone) 1 alpha subcomplex]; NDUF13 [NADH dehydrogenase (ubiquinone) 1 alpha/beta subcomplex]; NDUD1 [NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 2]; NDUD4 [neural precursor cell expressed, developmentally down-regulated 4]; NEFL [neurofilament, light polypeptide]; NEFM [neurofilament, medium polypeptide]; NEGR1 [neural growth regulator 1]; NEK6 [NIMA (never in mitosis gene a)-related kinase 6]; NELF [nasal embryonic 11HR factor]; NEL1 [NEL-like 1 (chicken)]; NES [nestin]; NEU1 [sialidase 1 (glycosomal sialidase)]; NEUROD1 [neuronal differentiation 1]; NF1 [neurofibromin 1]; NF2 [neurofibromin 2 (merlin)]; NFAT5 [nuclear factor of activated T-cells 5, toxicity-responsive]; NFATC1 [nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1]; NFATC2 [nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2]; NFATC4 [nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 4]; NFE2L2 [nuclear factor (erythroid-derived 2)-like 2]; NFKB1 [nuclear factor of kappa light polypeptide gene enhancer in B-cells 1]; NFKB2 [nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)]; NFKBIA [nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha]; NF-kB [nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta]; NFkB1 [nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1]; NFU1 [NFU1 iron-sulfur cluster scaffold homolog (S. cer-
evisiae): NGF (nerve growth factor receptor (TNFR superfamily, member 16)); NHEJ1 [nonhomologous end-joining factor 1]; NID1 [nidogen 1]; NKP [NKpB activating protein]; NKX2-1, NK2 homebox 1); NKX2-3 [NK2 transcription factor related, locus 3 (Drosophila)]; NLRP3 [NLR family, pyrin domain containing 3]; NMB [neuromedin B]; NME1 [non-metastatic cells 1, protein (NM23A) expressed in]; NME2 [non-metastatic cells 2, protein (NM23B) expressed in]; NMU [neuromedin U]; NNAT [neuroatin]; NOD1 [nucleotide-binding oligomerization domain containing 1]; NOD2 [nucleotide-binding oligomerization domain containing 2]; NONO [non-POU domain containing, octamer-binding]; NOS1 [nitric oxide synthase 1 (neuronal)]; NOS2 [nitric oxide synthase 2, inducible]; NOS3 [nitric oxide synthase 3 (endothelial cell)]; NOTCH1 [Notch homolog 1, translocation-associated (Drosophila)]; NOTCH2 [Notch homolog 2 (Drosophila)]; NOTCH3 [Notch homolog 3 (Drosophila)]; NOTCH4 [Notch homolog 4 (Drosophila)]; NOX1 [NADPH oxidase 1]; NOX3 [NADPH oxidase 3]; NOX4 [NADPH oxidase 4]; NOX5 [NADPH oxidase, EF-hand calcium binding domain 5]; NPAT [nuclear protein, ataxia-telangiectasia locus]; NPC1 [Niemann-Pick disease, type C1]; NPC1 L1 [NPC1 (Niemann-Pick disease, type C1, gene-like 1)]; NPC2 [Niemann-Pick disease, type C2]; NPHS1 [nephrosis, 1 congenital, Finnish type (nephrotic)]; NPHS2 [nephrosis 2, idiopathic, steroid-resistant (podocin)]; NPLOC4 [nuclear protein localization 4 homolog (S. cerevisiae)]; NPM1 [nucleophosmin (nucleolar phosphoprotein B23, numatrion)]; NPPA [natriuretic peptide precursor A]; NPPB [natriuretic peptide precursor B]; NPPC [natriuretic peptide precursor C]; NPR1 [natriuretic peptide receptor A (guanylate cyclase A (natriuretic peptide receptor A))]; NPR3 [natriuretic peptide receptor C (guanylate cyclase C (natriuretic peptide receptor C))]; NPS [neuropeptide S]; NPSR1 [neuropeptide S receptor 1]; NPY [neuropeptide Y]; NPY2R [neuropeptide Y receptor Y2]; NQO1 [NAD(P)H dehydrogenase, quinone 1]; NROB1 [nuclear receptor subfamily 0, group B, member 1]; NR1H2 [nuclear receptor subfamily 1, group H, member 2]; NR1H3 [nuclear receptor subfamily 1, group H, member 3]; NR1H4 [nuclear receptor subfamily 1, group H, member 4]; NR1H2 [nuclear receptor subfamily 1, group I, member 2]; NR1H3 [nuclear receptor subfamily 1, group I, member 3]; NR2F2 [nuclear receptor subfamily 2, group F, member 2]; NR3C1 [nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor)]; NR3C2 [nuclear receptor subfamily 3, group C, member 2]; NR4A1 [nuclear receptor subfamily 4, group A, member 1]; NR4A3 [nuclear receptor subfamily 4, group A, member 3]; NR5A1 [nuclear receptor subfamily 5, group A, member 1]; NRF1 [nuclear respiratory factor 1]; NRG1 [neuregulin 1]; NRP1 [nuclear receptor interacting protein 1]; NRP2 [nuclear receptor interacting protein 2]; NRP1 [neuropilin 1]; NSD1 [nuclear receptor binding SET domain protein 1]; NSDHL [NAD(P) dependent steroid dehydrogenase-like]; NSF [N-ethylmaleimide-sensitive factor]; NT5E [5'-nucleotidase, ecto (CD73)]; NTAN1 [N-terminal asparagine amidase]; NT3T [neurotrophin 3]; NT4F [neurotrophin 4]; NTN1 [netrin 1]; NTRK1 [neurotrophic tyrosine kinase, receptor, type 1]; NTRK2 [neurotrophic tyrosine kinase, receptor, type 2]; NTRK3 [neurotrophic tyrosine kinase, receptor, type 3]; NTS [neurotensin]; NUCB2 [neucoebin 2]; NUDT1 [nudix (nucleoside diphosphate linked moiety X)-type motif 1]; NUDT2 [nudix (nucleoside diphosphate linked moiety X)-type motif 2]; NUDT16 [nudix (nucleoside diphosphate linked moiety X)-type motif 6]; NUFIP2 [nuclear fragile X mental retardation protein interacting protein 2]; NUP98 [nucleoprin 98 kDa]; NUXF1 [nuclear RNA export factor 1]; OCA2 [oculocutaneous albinism II]; OCLN [oculitis]; ODC1 [ornithine decarboxylase 1]; ODF1 [oral-facial-digital syndrome 1]; OGDH [oxoglutarate (alpha-ketoglutarate) dehydrogenase (lipoamide)]; OGG1 [8-oxoguanine DNA glycosylase]; OTG1 [O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylgalcosaminyl transferase); OLR1 [oxidized low density lipoprotein (lectin-like) receptor 1]; OMP [olfactory marker protein]; ONECUT2 [one cut homeobox 2]; OPN3 [opsin 3]; OPRIK1 [opioid receptor, kappa 1]; OPRM1 [opioid receptor, mu 1]; OPTN [optineurin]; OR2B1 [olfactory receptor, family 2, subfamily B, member 11]; ORMDL3 [ORM1-like 3 (S. cerevisiae)]; OSBP [oxysterol binding protein]; OSGIN2 [oxidative stress induced growth inhibitor family member 2]; OSM [oncostatin M]; OTC [ornithine carbamoyltransferase]; OTO1 [otoetin 2]; OTO2 [otoetin 2]; OTO3 [otoetin 3]; OTUD1 [OTU domain containing 1]; OX32 [oxidase (cytochrome c) assembly-1-like]; OXR1 [oxoacid oxidase (OXE) receptor 1]; OXT [oxytocin, prepropeptide]; OXTR [oxytocin receptor]; P2RX7 [purinergic receptor P2X, ligand-gated ion channel, 7]; P2RY1 [purinergic receptor P2Y, G-protein coupled, 1]; P2RY12 [purinergic receptor P2Y, G-protein coupled, 12]; P2RY14 [purinergic receptor P2Y, G-protein coupled, 14]; P2RY2 [purinergic receptor P2Y, G-protein coupled, 2]; P4HA2 [prolyl 4-hydroxylase, alpha polypeptide II]; P4H15 [prolyl 4-hydroxylase, beta polypeptide]; P4HTM [prolyl 4-hydroxylase, transmembrane (endoplasmic reticulum)]; PA2PC1 [poly(A) binding protein, cytoplasmic 1]; P4CXS [protein kinase C and casein kinase substrate in neurons 3]; PAEP [progestagen-associated endometrial protein]; PAFAH1B1 [platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 (45 kDa)]; PAH [phenylalanine hydroxylase]; PAC [protein (Cdc42/Rac)-activated kinase 1]; PAC2 [protein (Cdc42/Rac)-activated kinase 2]; PAC3 [protein (Cdc42/Rac)-activated kinase 3]; PAME [peptidylglycine alpha-amidating monooxygenase]; PAPP [pregnancy-associated plasma protein A, pappalasin 1]; PARG [poly(ADP-ribose) glycohydrolase]; PARP2 [parkinson disease (autosomal recessive, juvenile) 2, parkin]; PARP1 [poly(ADP-ribose) polymerase 1]; PARW [PRKC, apoptosis, WT1, regulator]; PAX2 [paired box 2]; PAX3 [paired box 3]; PAX5 [paired box 5]; PAX6 [paired box 6]; PAXIP1 [PAX interacting (with transcription-activation domain) protein 1]; PC [pyruvate carboxylase]; PCC [pro-pionyl Coenzyme A carboxylase, alpha polypeptide]; PCCB [pro-pionyl Coenzyme A carboxylase, beta polypeptide]; PCDH11 [protochondrin 1]; PCK1 [phosphoenolpyruvate carboxykinase 1 (soluble)]; PCMB [pericentriolar material 1]; PCNA [pologenizing cell nucleus antigen]; PCNT [pericentrin]; PCSK1 [proprotein convertase subtilisin/kexin type 1]; PCSK6 [proprotein convertase subtilisin/kexin type 6]; PCSK7 [proprotein convertase subtilisin/kexin type 7]; PCYT1A [phosphate cytidylyltransferase 1, choline, alpha]; PCYT2 [phosphate cytidylyltransferase 2, ethanolamine]; PDCD1 [programmed cell death 1]; PDCD1L1 [programmed cell death 1 ligand 2]; PDCD6 [programmed cell death 6]; PDE3B [phosphodiesterase 3B, cGMP-inhibited]; PDE4A [phosphodiesterase 4A, cAMP-specific (phosphodiesterase E2 ducne homolog, Drosophila)]; PDE4B [phos-
phodiesterase 4B, cAMP-specific (phosphodiesterase 4E
dunce homolog, Drosophila); PDE4D [phosphodiesterase
4D, cAMP-specific (phosphodiesterase E3 dunce homolog,
Drosophila)]; PDE7A [phosphodiesterase 7A]; PDGFA
[platelet-derived growth factor alpha polypeptide]; PDGFβ
[platelet-derived growth factor beta polypeptide (sinnian sar-
coma viral (v-sis) oncogene homolog)]; PDGFRα [platelet-
derived growth factor receptor alpha, polypeptide]; PDGFRβ
[platelet-derived growth factor receptor beta, polypeptide];
PDI A2 [protein disulfide isomerase family A, member 2];
PDI A3 [protein disulfide isomerase family A, member 3];
PDK1 [pyruvate dehydrogenase kinase, isozyme 1];
PDK1M1 [PDZ and LIM domain 1]; PDLIM5 [PDZ and LIM
domain 5]; PDLIM7 [PDZ and LIM domain 7 (enigma)];
PDP1 [pyruvate dehydrogenase phosphatase catalytic subunit
1]; PDX1 [pancreatic and duodenal homeobox 1]; PDKK
[pyridoxal (pyridoxine, vitamin B6) kinase]; PDYN [pro-
dynorphin]; PECAM1 [platelet/endothelial cell adhesion
molecule]; PEMT [phosphatidylethanolamine N-methyl-
transferase]; PENK [penenkephalin]; PEPD [peptide D];
PER1 [period homolog 1 (Drosophila)]; PEX1 [peroxisomal
biogenesis factor 10]; PEX10 [peroxisomal biogenesis factor
10]; PEX12 [peroxisomal biogenesis factor 12]; PEX13
[peroxisomal biogenesis factor 13]; PEX14 [peroxisomal
biogenesis factor 14]; PEX16 [peroxisomal biogenesis factor
16]; PEX19 [peroxisomal biogenesis factor 19]; PEX2 [peroxi-
somal biogenesis factor 2]; PEX26 [peroxisomal biogenesis
factor 26]; PEX3 [peroxisomal biogenesis factor 3]; PEX5
[peroxisomal biogenesis factor 5]; PEX6 [peroxisomal biog-
genesis factor 6]; PEX7 [peroxisomal biogenesis factor 7];
PF4 [platelet factor 4]; PFAS [phosphoribosylformylglycin-
aminidine synthase]; PFDN4 [prefoldin subunit 4]; PFIN1 [pro-
filin 1]; PCG [progranulin (psenogen C)]; PGD [pyro-
gluconate dehydrogenase]; PGF [placental growth factor];
PGK1 [phosphoglycerate kinase 1]; PGM1 [phosphoglu-
cutase 1]; PGR [progestrone receptor]; PHB [prohibitin];
PHEX [phosphate regulating endopeptidase homolog, X-linked];
PHF11 [proteolipid protein 11]; PHOX2B [paired-like homeobox 2B]; PHTF1 [putative homeodomain transcription
factor 1]; PHYH [phytyl-CoA 2-hydroxylase]; PHYHIP [phytyl-CoA 2-hydroxylase interacting protein];
P13 [peptidase inhibitor 3, skin-derived]; PIGA [phosphatidylinositol glycine anchor biosynthesis, class A];
PIGK [polymorphic immunoglobulin receptor]; PIK3CA2
[phosphoinositide-3-kinase, class 2, alpha polypeptide];
PIK3CB2 [phosphoinositide-3-kinase, class 2, beta polypeptide];
PIK3CG2 [phosphoinositide-3-kinase, class 2, gamma polypeptide];
PIK3CC3 [phosphoinositide-3-kinase, class 3];
PIK3CA [phosphoinositide-3-kinase, catalytic, alpha polypeptide];
PIK3CB [phosphoinositide-3-kinase, catalytic, beta polypeptide];
PIK3CD [phosphoinositide-3-kinase, catalytic, delu polypeptide];
PIK3CG [phosphoinositide-3-kinase, catalytic, gamma polypeptide];
PIK3R1 [phosphoinositide-3-kinase, regulatory subunit 1 (alpha)];
PIK3R2 [phosphoinositide-3-kinase, regulatory subunit 2 (beta)];
PIK3R3 [phosphoinositide-3-kinase, regulatory subunit 3 (gamma)];
PIKFYVE [phosphoinositide kinase, FYVE finger containing];
PIM [pim3/4/5 kinase]; PIP [proline- and dipeptide; PIP5K1 [phosphati-
dylinositol-4-phosphate 5-kinase-like 1]; PIP5K1N1 [phos-
phatidylinositol-4-phosphate transfer, membrane-associat
ated]; PIPTRM1 [pitrilysin metalloproteinase 1]; PITTX2 [pitted-homodomain 2];
PKD2 [polycystic kidney disease 2 (auto-
somal dominant)]; PKLR [pyruvate kinase, liver and RBC];
PKM2 [pyruvate kinase, muscle]; PKN1 [protein kinase N1];
PL-5283 [PL-5283 protein]; PLAAIB [phospholipase A2, group
1B (pancreas)]; PLAG2A [phospholipase A2, group
IIA (platelets, synovial fluid)]; PLAG2D [phospholipase A2,
group IID]; PLAG4A [phospholipase A2, group IVA
(eyosolc, calcium-dependent)]; PLAG6 [phospholipase A2,
group V1 (eyosolc, calcium-independent)]; PLAG7
[phospholipase A2, group VII (platelet-activating factor
acylhydrolase, plasma)]; PLAR1 [phospholipase A2
receptor 1, 180 kDa]; PLAT [plasminogen activator, tissue];
PLAU [plasminogen activator, urokinase]; PLAR [plasmin-
genator activator, urokinase receptor]; PLCB1 [phospholipase
C, beta 1 (phosphoinoside-specific)]; PLCB2 [phospholipase
C, beta 2]; PLCB4 [phospholipase C, beta 4]; PLCD1
[phospholipase C, delta 1]; PLCG1 [phospholipase C, gamma
1]; PLCG2 [phospholipase C, gamma 2 (phosphatidy-
dinositol-specific)]; PLD1 [phospholipase D1, phosphatidy-
lcholine-specific]; PLEC [lecithin]; PLEK [leeknestrin];
PLG [plasminogen]; PLIN1 [perilipin 1]; PLK1 [polo-like
kinase 1 (Drosophila)]; PLK2 [polo-like kinase 2 (Dros-
ophila)]; PLK3 [polo-like kinase 3 (Drosophila)]; PLP1 [pro-
teopid protein 1]; PLTP [phospholipid transfer protein];
PMAIP1 [phorbol-12-myristate-13-acetate-induced protein];
PMCH [pro-melanin-concentrating hormone]; PML [pro-
myelocytic leukemia]; PMP22 [peripheral myelin protein
22]; PMS2 [PMS2 postmitotic segregation increased 2 (S.
cerevisiae)]; PNPLA [peroxisomal lipase]; PNMA3 [paracan-
ecoid antigen MA3]; PNMT [phenylethanolamine N-methyl-
transferase]; PNP [purine nucleoside phosphorylase];
POLB [polymerase (DNA-directed), beta]; POLD3 [poly-
merase (DNA-directed), delta 3, accessory subunit];
POLD4 [polymerase (DNA-directed), delta 4]; POLH [poly-
merase (DNA directed), eta]; POL [polymerase (DNA directed),
lambda]; POLR2A [polymerase (RNA II) (DNA directed)
polypeptide A, 220 kDa]; POLR2B [polymerase (RNA I)
(DNA directed) polypeptide B, 140 kDa]; POLR2C [poly-
merase (RNA II) (DNA directed) polyepide C, 33 kDa];
POLR2D [polymerase (RNA II) (DNA directed) polypeptide
D]; POLR2E [polymerase (RNA II) (DNA directed) poly-
peptide E, 25 kDa]; POLR2F [polymerase (RNA II) (DNA
directed) polypeptide F]; POLR2G [polymerase (RNA II)
(DNA directed) polypeptide G]; POLR2H [polymerase
(RNA II) (DNA directed) polypeptide H];
POLR2I [polymerase (RNA II) (DNA directed) polypeptide
I, 14.5 kDa]; POLR2J [polymerase (RNA II) (DNA directed)
polypeptide J, 13.3 kDa]; POLR2K [polymerase (RNA II) (DNA
directed) polyepide K, 7.0 kDa]; POLR2L [polymerase
(RNA II) (DNA directed) polypeptide L, 7.6 kDa];
POMC [proopiomelanocortin]; POMT1 [protein-O-mannosyltrans-
ferase 1]; PON1 [paraoxonase 1]; PON2 [paraoxonase 2];
PON3 [paraoxonase 3]; POSTN [perioserin, osteoblast
specific factor]; POT1 [POT1 protection of telomeres 1 homol-
og (S. pombe)]; POU2AF1 [POU class 2 associating factor 1];
POU2F1 [POU class 2 homeobox 1]; POU2F2 [POU class
2 homeobox 2]; POU5F1 [POU class 5 homeobox 1];
PPI [pyrophosphatase (inorganic)]; PPARA [peroxisome
proliferator-activated receptor alpha]; PPARD [peroxisome
proliferator-activated receptor delta]; PPARG [peroxisome
proliferator-activated receptor gamma];
PPARCG1A [peroxisome proliferator-activated receptor gamma, coactiv-
ator 1 alpha]; PPAR [pyruvate dehydrogenase amidotel-
transf erase]; PPRP [pro-protein basic (chemokine
(C—C—C motif) ligand 7)]; PPT1 [protein tyrosine phos-
phatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 1; PPLA [peptidylprolyl isomerase A (cyclophilin A)]; PPIB [peptidylprolyl isomerase B (cyclophilin B)]; PPIG [peptidylprolyl isomerase G (cyclophilin G)]; PPDX [protoporphyrinogen oxidase]; PPP1CB [protein phosphatase 1, catalytic subunit, beta isozyme]; PPP1R12A [protein phosphatase 1, regulatory (inhibitor) subunit 12A]; PPP1R2 [protein phosphatase 1, regulatory (inhibitor) subunit 2]; PPP2R1B [protein phosphatase 2, regulatory subunit A, beta]; PPP2R2B [protein phosphatase 2, regulatory subunit B, beta]; PPP2R4 [protein phosphatase 2A activator, regulatory subunit 4]; PPP6C [protein phosphatase 6, catalytic subunit]; PPT1 [phosphatidylinositol-thioesterase 1]; PPY [pancreatic polypeptide]; PRDM1 [PR domain containing 1, with 2 NFI domain]; PRDM2 [PR domain containing 2, with NFI domain]; PRDX2 [peroxiredoxin 2]; PRDX3 [peroxiredoxin 3]; PRDX5 [peroxiredoxin 5]; PRF1 [perforin 1 (pore forming protein)]; PRG2 [prostaglandin C2, bone marrow (natural killer cell) activator, eosinophil granule major basic protein]; PRG4 [prealbumin 4]; PRIM1 [primase, DNA, polypeptide 1 (49 kDa)]; PRKAA1 [protein kinase, AMP-activated, alpha 1 catalytic subunit]; PRKAA2 [protein kinase, AMP-activated, alpha 2 catalytic subunit]; PRKAB1 [protein kinase, AMP-activated, beta 1 non-catalytic subunit]; PRKACB [protein kinase, cAMP-dependent, catalytic, alpha]; PRKACG [protein kinase, cAMP-dependent, catalytic, beta]; PRKAG1 [protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)]; PRKAR1A [protein kinase, cAMP-dependent, regulatory, type I, alpha]; PRKAR2B [protein kinase, cAMP-dependent, regulatory, type II, beta]; PRKCA [protein kinase, cAMP-dependent, regulatory, type C, beta]; PRKCD [protein kinase C, delta]; PRKCE [protein kinase C, epsilon]; PRKCG [protein kinase gamma, PRKCH [protein kinase C, eta]; PRKCI [protein kinase C, iota]; PRKCC [protein kinase C, beta]; PRKCI [protein kinase C, gamma]; PRKDL1 [protein kinase D1]; PRKDK3 [protein kinase D3]; PRKDC [protein kinase, DNA-activated, catalytic polypeptide; also known as DNA PK]; PRKGI [protein kinase, cGMP-dependent, type I]; PRKRIR [protein-kinase, interferon-inducible double stranded RNA dependent inhibitor, repressor of (PS8 repressor)]; PRL [prolactin]; PRLR [prolactin receptor]; PRNP [prion protein]; PROC [protein C (inactivator of coagulation factors Va and Vlla)]; PRODH [proline dehydrogenase (oxidase)]; PIK [phosphatidylinositol (4)-kinase-1]; PIKO1 [protein kinase C]; PIK3C2B [protease, serine, 1 (trypsin)]; PIK3C2G [protease, serine, 2 (trypsin 2)]; PIK3C4 [protease, serine, 2 (testis)]; PIK3C5 [protease, serine, 3]; PRTN3 [proteinase 3]; PSAP [prosaposin]; PSEN1 [presenilin 1]; PSEN2 [presenilin 2 (Alzheimer disease 4)]; PSMA1 [proteasome (prosome, macropain) subunit, alpha type, 1]; PSMA2 [proteasome (prosome, macropain) subunit, alpha type, 2]; PSMA3 [proteasome (prosome, macropain) subunit, alpha type, 3]; PSMA5 [proteasome (prosome, macropain) subunit, alpha type, 5]; PSMA6 [proteasome (prosome, macropain) subunit, alpha type, 6]; PSMA7 [proteasome (prosome, macropain) subunit, alpha type, 7]; PSMB10 [proteasome (prosome, macropain) subunit, beta type, 10]; PSMB2 [proteasome (prosome, macropain) subunit, beta type, 2]; PSMB4 [proteasome (prosome, macropain) subunit, beta type, 4]; PSMB5 [proteasome (prosome, macropain) subunit, beta type, 5]; PSMB6 [proteasome (prosome, macropain) subunit, beta type, 6]; PSMB8 [proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)]; PSMB9 [proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)]; PSMC3 [proteasome (prosome, macropain) subunit, ATPase, 3]; PSMC4 [proteasome (prosome, macropain) subunit, ATPase, 4]; PSMC6 [proteasome (prosome, macropain) subunit, ATPase, 6]; PSMD4 [proteasome (prosome, macropain) subunit, non-ATPase, 4]; PSMD9 [proteasome (prosome, macropain) subunit, non-ATPase, 9]; PSME1 [proteasome (prosome, macropain) activator subunit 1 (PA28 alpha)]; PSME2 [proteasome (prosome, macropain) activator subunit 3 (PA28 gamma); K1]; PSMG2 [proteasome (prosome, macropain) assembly chaperone 2]; PSORS1C1 [psoriasis susceptibility 1 candidate 1]; PSTPIP1 [proline-serine-threonine phosphatase interacting protein 1]; PTAFR [platelet-activating factor receptor]; PTB1P1 [polypyrroleiminetract binding protein 1]; PTCH1 [patched homolog 1 (Drosophila)]; PTEN [phosphatase and tensin homolog]; PTGDR [prostaglandin D2 receptor (DP)]; PTGDS [prostaglandin D2 synthase 21 kDa (brain)]; PTGER1 [prostaglandin E receptor 1 (subtype EP1), 42 kDa]; PTGER2 [prostaglandin E receptor 2 (subtype EP2), 53 kDa]; PTGER3 [prostaglandin E receptor 3 (subtype EP3)]; PTGER4 [prostaglandin E receptor 4 (subtype EP4)]; PTGES [prostaglandin E synthase]; PTGFR [prostaglandin F receptor (FP)]; PTGR1 [prostaglandin 12 (prostacyclin) receptor (IP)]; PTGSI [prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)]; PTGS2 [prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)]; PTH [parathyroid hormone]; PTHLH [parathyroid hormone-like hormone]; PTK2 [PTK2 protein tyrosine kinase 2]; PTK2B [PTK2B protein tyrosine kinase 2 beta]; PTK7 [PTK7 protein tyrosine kinase 7]; PTMS [parathyminosin]; PTN [pleiotrophin]; PTEN1 [protein tyrosine phosphatase, non-receptor type 1]; PTEN11 [protein tyrosine phosphatase, non-receptor type 11]; PTEN12 [protein tyrosine phosphatase, non-receptor type 12]; PTPN2 [protein tyrosine phosphatase, non-receptor type 2]; PTPN22 [protein tyrosine phosphatase, non-receptor type 22 (lymphoid)]; PTPN6 [protein tyrosine phosphatase, non-receptor type 6]; PTPRC [protein tyrosine phosphatase, receptor type, C]; PTPRD [protein tyrosine phosphatase, receptor type, D]; PTPRE [protein tyrosine phosphatase, receptor type, E]; PTPRJ [protein tyrosine phosphatase, receptor type, J]; PTPRN [protein tyrosine phosphatase, receptor type, N]; PTPRT [protein tyrosine phosphatase, receptor type, T]; PTPRZ [protein tyrosine phosphatase, receptor type, U]; PUTF [polymerase 1 and transcript release factor]; PTS [6-pyruvoyl-tetrahydropterin synthase]; PTTG1 [pituitary tumor-transforming 1]; PTX3 [pentraxin 3, long]; PUS10 [pseudouridylate synthase 10]; PXK [PX domain containing serine/threonine kinase]; PXN [paxillin]; PYCR1 [pyrroline-5-carboxylate reductase 1]; PYCRL2 [pyrroline-5-carboxylate reductase family, member 2]; PYGB [phosphorylase, glycogen; brain]; PYGM [phosphorylase, glycogen, muscle]; PYY [peptide YY]; PZF [pregnancy-zone protein]; QDPR [quinoid dihydropterin reductase]; RAB11A [RAB11A, member RAS oncogene family]; RAB11FIP1 [RAB11 family interacting protein 1 (class I)]; RAB27A [RAB27A, member RAS oncogene family]; RAB37 [RAB37, member RAS oncogene family]; RAB39 [RAB39, member RAS oncogene family]; RAB7A [RAB7A, member RAS oncogene family]; RAB9A [RAB9A, member RAS oncogene family]; RAC1 [ras-re...
lated C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); RAC2 [ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)]; RAD7 [RAD17 homolog (S. pombe)]; RAD50 [RAD50 homolog (S. cerevisiae)]; RAD51 [RAD51 homolog (E. coli) (S. cerevisiae)]; RAD51C [RAD51 homolog C (S. cerevisiae)]; RAD51L1 [RAD51-like 1 (S. cerevisiae)]; RAD51L3 [RAD51-like 3 (S. cerevisiae)]; RAD54L [RAD54-like (S. cerevisiae)]; RADA9 [RADS homolog A (S. pombe)]; RAF1 [v-raf-1 murine leukemia viral oncogene homolog 1]; RAG1 [recombination activating gene 1]; RAC2 [recombination activating gene 2]; RAN [RAN, member RAS oncogene family]; RANBP1 [RAN binding protein 1]; RAP1A [RAP1A, member of RAS oncogene family]; RAPGEF4 [Rap guanine-nucleotide exchange factor (GEP) 4]; RARA [retinoic acid receptor, alpha]; RARB [retinoic acid receptor, beta]; RARG [retinoic acid receptor, gamma]; RARRES2 [retinoic acid receptor responder (tazarotene induced) 2]; RAS [arginine, yRNA synthetase]; RASA1 [RAS p21 protein activator (GTPase activating protein 1)]; RASGRF1 [RAS guanyl releasing protein 1 (calcium and DAG-regulated)]; RASGRF2 [RAS guanyl releasing protein 2 (calcium and DAG-regulated)]; RASGRF4 [RAS guanyl releasing protein 4]; RASSF1 [Ras association (RalGDS/AF-6) domain family member 1]; RB1 [retinoblastoma 1]; RBBP4 [retinoblastoma binding protein 4]; RBBP8 [retinoblastoma binding protein 8]; RBL1 [retinoblastoma-like 1 (p107)]; RBL2 [retinoblastoma-like 2 (p130)]; RBP4 [retinol binding protein 4, plasma]; RBX1 [ring-box 1]; RCBT1 [regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 1]; RCN1 [reticulocalbin 1, EF-hand calcium binding domain]; RCN2 [reticulocalbin 2, EF-hand calcium binding domain]; RDX [radixin]; RECK [reversion-inducing-cysteine-rich protein with kazal motif]; RECQL [RECQ protein-like (DNA helicase Q1-like)]; RECQL4 [RECQ protein-like 4]; RECQL5 [RECQ protein-like 5]; REG1A [regenerating islet-derived 1 alpha]; REG3A [regenerating islet-derived 3 alpha]; REG4 [regenerating islet-derived family, member 4]; REL [c-rel reticulohendrosis viral oncogene homolog (avian)]; RELA [c-rel reticulohendrosis viral oncogene homolog A (avian)]; RELB [c-rel reticulohendrosis viral oncogene homolog B]; REN [renin]; RET [ret proto-oncogene]; RETN [resistin]; RETNLB [resistin like beta]; RFC1 [replication factor C (activator 1) 1, 145 kDa]; RFC2 [replication factor C (activator 1) 2, 40 kDa]; RFC3 [replication factor C (activator 1) 3, 38 kDa]; RFX1 [regulatory factor X, 1 (influences IL-1 alpha class I expression)]; RFX5 [regulatory factor X, 5 (influences IL-1A class II expression)]; RFXANK [regulatory factor X-associated ankyrin-containing protein]; RFXAP [regulatory factor X-associated protein]; RGS18 [regulator of G-protein signaling 18]; RHAG [Ras-associated glycoprotein]; RHDF [Rh blood group, D antigen]; RHOD [rhodopsin]; RHOA [ras homolog gene family, member A]; RHOD [ras homolog gene family, member D]; RIF1 [RAP1 interacting factor homolog (yeast)]; RIK1 [receptor (TRF8)-interacting serine-threonine kinase 1]; RIPK2 [receptor-interacting serine-threonine kinase 2]; RLBP1 [retinaldehyde binding protein 1]; RN1L [relaxin 1]; RN2L [relaxin 2]; RM1 [RM1, Rac class I homolog (murine) 1]; RNA [RNAse mRNA]; RNAK1 [ribonuclease, RNAse A family, 1 (pancreatic) or RNAse A family, 2 (liver, c-Jun-NH2-deriv. neurotoxin)]; RNAE2 [ribonuclease, RNAse A family, 2 (liver, c-Jun-NH2-deriv. neurotoxin)]; RNAE3 [ribonuclease, RNAse A family, 3 (caspase 3 activating domain)]; RNASEH1 [ribonuclease H1]; RNASEH2A [ribonuclease H2, subunit A]; RNASEL [ribonuclease L (2’-5’-oligoadenylate synthetase-dependent)]; RNASEN [ribonuclease type III, nuclear]; RNF123 [ring finger protein 123]; RNF13 [ring finger protein 13]; RNF135 [ring finger protein 135]; RNF138 [ring finger protein 138]; RNF4 [ring finger protein 4]; RNH1 [ribonuclease/Angiogenin inhibitor 1]; RNPC3 [RNA-binding region (RNPI, RNMR) containing 3]; RNPEP [arginyl aminopeptidase (aminopeptidase B)]; ROCK1 [Rho-associated, coiled-coil containing protein kinase 1]; ROM1 [retinal outer segment membrane protein 1]; ROR2 [receptor tyrosine kinase-like orphan receptor 2]; RORA [ROR-related orphan receptor A]; RPA1 [replication protein A, 70 kDa]; RPA2 [replication protein A, 32 kDa]; RPGRIP1 [RP-GRIP1-like]; RP1P1 [ribosomal protein, large, P1]; RPS9 [ribosomal protein S19]; RPS6KA3 [ribosomal protein S6 kinase, 90 kDa, polyepitope 3]; RPS6KD1 [ribosomal protein S6 kinase, 70 kDa, polyepitope 1]; RPSA [ribosomal protein SA]; RBP1 [ribosomal binding protein 1 homolog 180 kDa (dog)]; RRML [ribonucleotide reductase M1]; RRMM2B [ribonucleotide reductase M2 B (TP53 inducible)]; RUNX1 [run-related transcription factor 1]; RUNX3 [run-related transcription factor 3]; RXRA [retinoid X receptor, alpha]; RXR [retinoid X receptor, beta]; RYR1 [ryanodine receptor 1 (skeletal)]; RYR3 [ryanodine receptor 3]; S100A1 [S100 calcium binding protein A1]; S100A12 [S100 calcium binding protein A12]; S100A4 [S100 calcium binding protein A4]; S100A7 [S100 calcium binding protein A7]; S100A8 [S100 calcium binding protein A8]; S100A9 [S100 calcium binding protein A9]; S100B [S100 calcium binding protein B]; S100G [S100 calcium binding protein G]; S1PR1 [sphingosine-1-phosphate receptor 1]; SAA1 [serum amyloid A1]; SAA4 [serum amyloid A4, constitutive]; SAFP [scalfold attachment factor B]; SAG [S-antigen; retina and pineal gland (arrestin)]; SAGE1 [sarcosine dehydrogenase]; SART3 [squamous cell carcinoma antigen recognized by T cells 3]; SBDS [Shwachman-Bodian-Diamond syndrome]; SBNO2 [trypsinogen homolog 2 (Drosophila) or SCAMP3 [secretory carrier membrane protein 3]; SOAP [SREBF chaperone]; SCARB1 [scavenger receptor class B member 1]; SCDC [stearyl-CoA desaturase (delta-9-desaturase)]; SCG2 [secretogranin II]; SCG3 [secretogranin III]; SCG5 [secretogranin V (7B2 protein)]; SCGB1A1 [secretoglobin, family 1A, member 1 (uteroglobin)]; SCGB3A2 [secretoglobin, family 3A, member 2]; SCN4A [sodium channel, voltage-gated, type IV, alpha subunit]; SCNN1A [sodium channel, nonvoltage-gated 1 alpha]; SCNN1G [sodium channel, nonvoltage-gated 1 gamm]; SCOC1 [SCO cytochrome oxidase deficient homolog 1 (yeast)]; SCO2 [SCO cytochrome oxidase deficient homolog 2 (yeast)]; SCP2 [sterol carrier protein 2]; SCT [secretin]; SDC1 [syndecan 1]; SDC2 [syndecan 2]; SDC4 [syndecan 4]; SDHB [succinate dehydrogenase complex, subunit B, iron sulfur (I)] or SDHD [succinate dehydrogenase complex, subunit D, integral membrane protein]; SECC14.2 [SECC14.2 (S. cerevisiae)]; SECC16A [SECC16 homolog A (S. cerevisiae)]; SECC23B [SECC23 homolog B (S. cerevisiae)]; SELESE [selectin F]; SELL [selectin F]; SELP [selectin P (granule membrane protein 140 kDa, antigen CD62)]; SELE-PLG [selectin P ligand]; SELEP5 [selectin 5]; SEPP1 [selemoprotein P, plasma]; SEPT5 [septin 5]; SEPT9 [septin 9]; SEPIS [Sep (O-phosphoserine) thRNA:Sec (serencysteine) thRNA synthase]; SERBP1 [SERPINE1 mRNA binding protein 1]; SERPINH1 [serpin peptidase inhibitor, clade A (alpha-1 antitrypsin, antitrypsin)
member 1]; SERPINA2 [serpin peptidase inhibitor, clade A (alpha-1 antiprotease, antitrypsin), member 2]; SERPINA3 [serpin peptidase inhibitor, clade A (alpha-1 antiprotease, antitrypsin), member 3]; SERPINA5 [serpin peptidase inhibitor, clade A (alpha-1 antiprotease, antitrypsin), member 5]; SERPINA6 [serpin peptidase inhibitor, clade A (alpha-1 antiprotease, antitrypsin), member 6]; SERPINA7 [serpin peptidase inhibitor, clade A (alpha-1 antiprotease, antitrypsin), member 7]; SERPINB1 [serpin peptidase inhibitor, clade B (ovublin), member 1]; SERPINB2 [serpin peptidase inhibitor, clade B (ovublin), member 2]; SERPINB3 [serpin peptidase inhibitor, clade B (ovublin), member 3]; SERPINB4 [serpin peptidase inhibitor, clade B (ovublin), member 4]; SERPINB5 [serpin peptidase inhibitor, clade B (ovublin), member 5]; SERPINB6 [serpin peptidase inhibitor, clade B (ovublin), member 6]; SERPINB9 [serpin peptidase inhibitor, clade B (ovublin), member 9]; SERPINC1 [serpin peptidase inhibitor, clade C (antithrombin), member 1]; SERPIND1 [serpin peptidase inhibitor, clade D (heparin cofactor), member 1]; SERPINE1 [serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 1]; SERPINE2 [serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2]; SERPINF2 [serpin peptidase inhibitor, clade F (alpha-2 antiplasmin, pigment epithelium derived factor), member 2]; SERPING1 [serpin peptidase inhibitor, clade G (C1 inhibitor), member 1]; SERPINH1 [serpin peptidase inhibitor, clade H (heat shock protein 47), member 1], (collagen binding protein 1)]; SET [SET nuclear oncogene]; SETDB2 [SET domain, bifurcated 2]; SETX [senataxin]; SFPQ [splicing factor proline/glutamine-rich (polypyrrolidine tract binding protein associated)]; SFRP1 [secreted frizzled-related protein 1]; SFRP2 [secreted frizzled-related protein 2]; SFRP5 [secreted frizzled-related protein 5]; STAP1 [surfactant protein A1]; STFB [surfactant protein B]; STFCP [surfactant protein C]; STFPD [surfactant protein D]; SGCA [sarcoglycan, alpha (50 kDa dystrophin-associated glycoprotein)]; SGCB [sarcoglycan, beta (43 kDa dystrophin-associated glycoprotein)]; SGK1 [serum/glucocorticoid regulated kinase 1]; SGSH [N-sulfoglycosamin sulfohydrolase]; SGTA [small glutamine-rich tetratricopeptide repeat (TPR)-containing, alpha]; SH2B1 [SH2B adaptor protein 1]; SH2B3 [SH2B adaptor protein 3]; SH2D1A [SH2 domain containing 1A]; SH2D4B [SH2 domain containing 4B]; SH3 KBP1 [SH3-domain kinase binding protein 1]; SHBG [sex hormone-binding globulin]; SHC1 [SRC (Shc homology 2 domain containing) transforming protein 1]; SHH [sonic hedgehog homolog (Drosophila)]; SHMT2 [serine hydroxymethyltransferase 2 (mitochondrial)]; SII [su-crane-isomaltase (alpha-glucoisidase)]; SIGIRR [single immunoglobulin and toll-interleukin 1 receptor (TIR) domain]; SIP1 [survival of motor neuron protein interacting protein]; SIPA1 [signal-induced proliferation-associated 1]; SIPPA [signal-regulatory protein alpha]; SIPPB2 [signal-regulatory protein beta 2]; SIRT1 [sirtuin (silent mating type information regulation 2 homolog) 1 (S. cerevisiae)]; SKIV2L [superkiller viridicatic activity 2-like (S. cerevisiae)]; SKP2 [S-phase kinase-associated protein 2 (p45)]; SLAMF1 [signaling lymphocyte activation molecule family member 1]; SLAMF6 [SLAM family member 6]; SLCA1A1 [solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1]; SLCA1A2 [solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2]; SLCA2A [solute carrier family 12 (sodium/potassium/chloride transporters), member 1]; SLCA2A2 [solute carrier family 12 (sodium/potassium/chloride transporters), member 2]; SLCA4A1 [solute carrier family 14 (urea transporter), member 1]; SLCA5A1 [solute carrier family 15 (oligopeptide transporter), member 1]; SLCA6A1 [solute carrier family 16, member 1 (monocarboxylic acid transporter 1)]; SLCA7A5 [solute carrier family 17 (anion/sugar transporters), member 5]; SLCA7A6 [solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 6]; SLCA7A7 [solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7]; SLCA9A1 [solute carrier family 19 (folute transporter), member 1]; SLCA1A [solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xg), member 1]; SLCA1A2 [solute carrier family 1 (glutamate/neuronal amino acid transporter), member 4]; SLCA1A3 [solute carrier family 22 (organic anion/urate transporter), member 12]; SLCA2A2 [solute carrier family 22 (organic cation transporter), member 2]; SLCA2A3 [solute carrier family 22, member 23]; SLCA2A3 [solute carrier family 22 (extraneuronal monoamine transporter), member 3]; SLCA2A4 [solute carrier family 22 (organic cation/epithelial membrane transporter), member 4]; SLCA2A5 [solute carrier family 22 (organic cation/carnitine transporter), member 5]; SLCA2A6 [solute carrier family 22 (organic anion transporter), member 6]; SLCA2A2 [solute carrier family 24 (sodium/potassium/calcium exchanger), member 2]; SLCA5A2 [solute carrier family 25 (mitochondrial carrier, citrate transporter), member 1]; SLCA5A20 [solute carrier family 25 (carnitine/acylcarnitine translocase), member 20]; SLCA5A3 [solute carrier family 25 (mitochondrial carrier, phosphate carrier), member 3]; SLCA5A32 [solute carrier family 25, member 32]; SLCA5A33 [solute carrier family 25, member 33]; SLCA5A4 [solute carrier family 25 (mitochondrial carrier, adenine nucleotide translocase), member 4]; SLCA6A4 [solute carrier family 26, member 4]; SLCA7A4 [solute carrier family 27 (fatty acid transporter), member 4]; SLCA8A1 [solute carrier family 28 (sodium-coupled nucleoside transporter), member 1]; SLCA2A1 [solute carrier family 2 (facilitated glucose transporter), member 1]; SLCA2A3 [solute carrier family 2 (facilitated glucose transporter), member 3]; SLCA2A4 [solute carrier family 2 (facilitated glucose transporter), member 4]; SLCA3A0 [solute carrier family 30 (zinc transporter), member 1]; SLCA3A8 [solute carrier family 30 (zinc transporter), member 8]; SLCA3A1 [solute carrier family 31 (copper transporters), member 1]; SLCA3A51 [solute carrier family 35 (Cmp5-ribose-5-phosphate transporter), member 1]; SLCA3A2 [solute carrier family 35 (UDP-galactose transporter), member 2]; SLCA3C1 [solute carrier family 35, member C1]; SLCA3F2 [solute carrier family 35, member F2]; SLCA3A9 [solute carrier family 39 (zinc transporter), member 3]; SLCA3A2 [solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2]; SLCA4A1 [solute carrier family 46 (folute transporter), member 1]; SLCA4A5 [solute carrier family 5 (sodium iodide symporter), member 5]; SLCA4A11 [solute carrier family 6 (neurotransmitter transporter, GABA), member 11]; SLCA6A14 [solute carrier family 6 (amino acid transporter), member 14]; SLCA6A19 [solute carrier family 6 (neutral amino acid transporter), member 19]; SLCA6A3 [solute carrier family 6 (neurotransmitter transporter, dopamine), member 3]; SLCA6A4 [solute carrier family 6 (neurotransmit-
drial]; TFAP2A [transcription factor AP-2 alpha (activating enhancer binding protein 2 alpha)]; TFF2 [trefoil factor 2]; TFF3 [trefoil factor 3 (intestinal)]; TFPI [tissue factor pathway inhibitor (lipoprotein-associated coagulation inhibitor)]; TFPT [TF3C (E2A) fusion partner (in childhood leukemia)]; TFR2 [transferrin receptor 2]; TFRC [transferrin receptor (p90, CD71)]; TG [thioglycolate]; TGFA [transforming growth factor, alpha]; TGFB1 [transforming growth factor, beta 1]; TGFB2 [transforming growth factor, beta 2]; TGFB3 [transforming growth factor, beta 3]; TGFBRI [transforming growth factor, beta receptor 1]; TGFBRII [transforming growth factor, beta receptor II (70/80 kDa)]; TGF1 [TGFB-induced factor homeobox 1 (K polypeptide epidermal type 1, protein-glutamine-gamma-glutamyltransferase)]; TGM2 [transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)]; TGM3 [transglutaminase 3 (E polypeptide, protein-glutamine-gamma-glutamyltransferase)]; TH1 [tyrosine hydroxylase]; THAP1 [THAP domain containing, apoptosis associated protein 1]; THBD [thrombomodulin]; THBS1 [thrombospondin 1]; THBS3 [thrombospondin 3]; THPO [thrombopoietin]; THY1 [Thy-1 cell surface antigen]; TIA1 [TIA1 cytotoxic granule-associated RNA binding protein]; TIE1 [tyrosine kinase with immunoglobulin-like and EGF-like domains 1]; TIMD4 [T-cell immunoglobulin and mucin domain containing 4]; TIMELESS [timeless homolog (Drosophila)]; TIMP1 [TIMP metalloproteinase inhibitor 1]; TIMP2 [TIMP metalloproteinase inhibitor 2]; TIMP3 [TIMP metalloproteinase inhibitor 3]; TRAP [toll-interleukin 1 receptor (TIR) domain containing adaptor protein]; TJPL1 [tight junction protein 1 (zona occludens 1)]; TK1 [thymidine kinase 1, soluble]; TK2 [thymidine kinase 2, mitochondrial]; TK1 [transketolase]; TLF [transducin-like enhancer of split 4 (E(sp1) homolog, Drosophila)]; TLR1 [toll-like receptor 1]; TLR10 [toll-like receptor 10]; TLR2 [toll-like receptor 2]; TLR3 [toll-like receptor 3]; TLR4 [toll-like receptor 4]; TLR5 [toll-like receptor 5]; TLR6 [toll-like receptor 6]; TLR7 [toll-like receptor 7]; TLR8 [toll-like receptor 8]; TLR9 [toll-like receptor 9]; TLRX1 [T-cell leukemia homeobox 1]; TNFSF4 [transmembrane 7 superfamily member 4]; TMEFD3 [transmembrane emp24 protein transport domain containing 3]; TMEFF2 [transmembrane protein with EGF-like and two follistatin-like domains 2]; TMEM132E [transmembrane protein 132E]; TMEM18 [transmembrane protein 18]; TMEM19 [transmembrane protein 19]; TMEM216 [transmembrane protein 216]; TMEM227 [transmembrane protein 27]; TMEM67 [transmembrane protein 67]; TMPO [thymopoietin]; TRPS1 [transmembrane protease, serine 15]; TRMSB4X [thymosin beta 4, X-linked]; TNC [tenascin C]; TNF [tumor necrosis factor (TNF superfamily, member 2)]; TNFAIP1 [tumor necrosis factor, alpha-induced protein 1 (endothelial)]; TNFAIP3 [tumor necrosis factor, alpha-induced protein 3]; TNFAIP6 [tumor necrosis factor, alpha-induced protein 6]; TNFRSF1A [tumor necrosis factor receptor superfamily, member 10a]; TNFRSF10B [tumor necrosis factor receptor superfamily, member 10b]; TNFRSF10C [tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain]; TNFRSF10D [tumor necrosis factor receptor superfamily, member 10d, decoy with truncated death domain]; TNFRSF11A [tumor necrosis factor receptor superfamily, member 11a, NFkB activator]; TNFRSF11B [tumor necrosis factor receptor superfamily, member 11b]; TNFRSF13B [tumor necrosis factor receptor superfamily, member 13B]; TNFRSF13C [tumor necrosis factor receptor superfamily, member 13C]; TNFRSF14 [tumor necrosis factor receptor superfamily, member 14 (herpesvirus entry mediator)]; TNFRSF17 [tumor necrosis factor receptor superfamily, member 17]; TNFRSF18 [tumor necrosis factor receptor superfamily, member 18]; TNFRSF1A [tumor necrosis factor receptor superfamily, member 1A]; TNFRSF1B [tumor necrosis factor receptor superfamily, member 1B]; TNFRSF21 [tumor necrosis factor receptor superfamily, member 21]; TNFRSF25 [tumor necrosis factor receptor superfamily, member 25]; TNFRSF4 [tumor necrosis factor receptor superfamily, member 4]; TNFRSF6B [tumor necrosis factor receptor superfamily, member 6b, decoy]; TNFRSF8 [tumor necrosis factor receptor superfamily, member 8]; TNFRSF9 [tumor necrosis factor receptor superfamily, member 9]; TNFSF10 [tumor necrosis factor (ligand) superfamily, member 10]; TNFSF11 [tumor necrosis factor (ligand) superfamily, member 11]; TNFSF12 [tumor necrosis factor (ligand) superfamily, member 12]; TNFSF13 [tumor necrosis factor (ligand) superfamily, member 13]; TNFSF13B [tumor necrosis factor (ligand) superfamily, member 13b]; TNFSF14 [tumor necrosis factor (ligand) superfamily, member 14]; TNFSF15 [tumor necrosis factor (ligand) superfamily, member 15]; TNFSF18 [tumor necrosis factor (ligand) superfamily, member 18]; TNFSF4 [tumor necrosis factor (ligand) superfamily, member 4]; TNFSF8 [tumor necrosis factor (ligand) superfamily, member 8]; TNFSF9 [tumor necrosis factor (ligand) superfamily, member 9]; TNKS [tanksyrase, TRAF1-interacting ankyrin-related ADP-ribose polymerase]; TNRC11 [trypsin C type 1 (slow)]; TNRC12 [trypsin I type 2 (skeletal, fast)]; TNRC13 [trypsin I type 3 (cardiac)]; TNRC13 [trypsin I t type 3 (skeletal, fast)]; TNPO1 [transportin 1]; TNS1 [tensin 1]; TNRX [tenesin Xb]; TOM1L2 [target of myb-1 like 2 (chicken)]; TOP1 [topoisomerase (DNA I)]; TOP1MT [topoisomerase (DNA I), mitochondrial]; TOP2A [topoisomerase (DNA II) alpha 170 kDa]; TOP2B [topoisomerase (DNA II) beta 180 kDa]; TOP3A [topoisomerase (DNA III) alpha]; TOPBP1 [topoisomerase (DNA II) binding protein 1]; TP53 [tumor protein p53]; TP53BP1 [tumor protein p53 binding protein 1]; TP53RK [TP53 regulating kinase]; TP63 [tumor protein p63]; TP73 [tumor protein p73]; TP552 [tumor protein D52]; TPH1 [tryptophan hydroxylase 1]; TPI1 [triosephosphate isomerase 1]; TPM1 [tropomyosin 1 (alpha)]; TPM2 [tropomyosin 2 (beta)]; TPM1 [tropomyosin 2 (beta)]; TPO [thyroid peroxidase]; TP1 [tropo peptide peptide I]; TP2 [tropo peptide peptide II]; TPR [tubulin polymerization promoting protein]; TPP3 [tubulin polymerization-promoting protein family member 3]; TPSAB1 [trophynase alpha/beta 1]; TPSB2 [trophynase beta 2 (gene/pseudogene)]; TPSD1 [trophynase delta 1]; TPSG1 [trophynase gamma 1]; TPF1 [tumor protein, translationally-controlled 1]; TRADD [TNFRSF1A-associated via death domain]; TRAF1 [TNF receptor-associated factor 1]; TRAF2 [TNF receptor-associated factor 2]; TRAF3 [TNF receptor-associated factor 3]; TRAF3P1P2 [TRAF3 interacting protein 2]; TRAF6 [TNF receptor-associated factor 6]; TRAP [TAF interacting protein]; TRAPP [trafficking protein particle complex 10]; TRDN [triad]; TREX1 [three prime repair exonuclease 1]; TRH [thyrotropin-releasing hormone]; TRIB1 [tribbles homolog 1 (Drosophila)]; TRIM21 [tripartite motif-containing 21]; TRIM22 [tripartite motif-containing 22]; TRIM26 [tripartite motif-containing 26]; TRIM28 [tripartite motif-containing 28]; TRIM29 [tripartite motif-containing 29]; TRIM68 [tripartite motif-containing 68]; TRPA1 [transient
receptor potential cation channel, subfamily A, member 1]; TRPC1 [transient receptor potential cation channel, subfamily C, member 1]; TRPC3 [transient receptor potential cation channel, subfamily C, member 3]; TRPC6 [transient receptor potential cation channel, subfamily C, member 6]; TRPM1 [transient receptor potential cation channel, subfamily M, member 1]; TRPM8 [transient receptor potential cation channel, subfamily M, member 8]; TRPS1 [trichorhinophalangeal syndrome 1]; TRPV1 [transient receptor potential cation channel, subfamily V, member 1]; TRPV4 [transient receptor potential cation channel, subfamily V, member 4]; TRPV5 [transient receptor potential cation channel, subfamily V, member 5]; TRPV6 [transient receptor potential cation channel, subfamily V, member 6]; TRRAP [transformation/transcription domain-associated protein]; TSC1 [tuberous sclerosis 1]; TSC2 [tuberous sclerosis 2]; TSC22D3 [TSC22 domain family, member 3]; TSG101 [tumor susceptibility gene 101]; TSHR [thyroid stimulating hormone receptor]; TSLP [thymic stromal lymphopoietin]; TSPAN7 [tetraspanin 7]; TSPO [translocator protein (18 kDa)]; TSSK2 [testis-specific serine kinase 2]; TSTA3 [tissue specific transplantation antigen P358]; TT1F2 [transcription termination factor, RNA polymerase II]; TTN [titin]; TTPA [t-cotatephrol (alpha) transfer protein]; TTR [transferrin]; TUBA1B [tubulin, alpha 1b]; TUBA4A [tubulin, alpha 4a]; TUBB [tubulin, beta]; TUBB1 [tubulin, beta 1]; TUBG1 [tubulin, gamma 1]; TWIST1 [twist homolog 1 (Drosophila)]; TWGS1 [twisted gastrulation homolog 1 (Drosophila)]; TXK [TXK tyrosine kinase]; TXN [thioredoxin]; TXN2 [thioredoxin 2]; TXNDC5 [thioredoxin domain containing 5 (endoplasmic reticulum)]; TXNDC9 [thioredoxin domain containing 9]; TXNIP [thioredoxin-interacting protein]; TXNRD1 [thioredoxin reductase 1]; TXNRD2 [thioredoxin reductase 2]; TYK2 [tyrosine kinase 2]; TYPM [thymidine phosphorylase]; TYSM [thymidylate synthetase]; TYR [tyrosinase (oculocutaneous albinism 1A)]; TYRO3 [TYRO3 protein tyrosine kinase]; TYROBP [TYRO protein tyrosine kinase binding protein]; TYRPI1 [tyrosine-related protein 1]; UBB [ubiquitin B]; UBC [ubiquitin C]; UBE2C [ubiquitin-conjugating enzyme E2C]; UBE2N [ubiquitin-conjugating enzyme E2N (UBC13 homolog, yeast)]; UBE2U [ubiquitin-conjugating enzyme E2U (putative)]; UBE3A [ubiquitin protein ligase E3A]; UBE4A [ubiquitin fusion factor E4A (UFD2 homolog, yeast)]; UCHL1 [ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)]; UCN [urocortin]; UCN2 [urocortin 2]; UCP1 [uncoupling protein 1 (mitochondrial, proton carrier)]; UCP2 [uncoupling protein 2 (mitochondrial, proton carrier)]; UCP3 [uncoupling protein 3 (mitochondrial, proton carrier)]; UFDC1 [ubiquitin fusion degradation 1 like (yeast)]; UGCG [UDP-glucose ceramide glucosyltransferase]; UGP2 [UDP-glucose pyrophosphorylase 2]; UGT1A1 [UDP glucuronosyltransferase 1 family, polypeptide A1]; UGT1A6 [UDP glucuronosyltransferase 1 family, polypeptide A6]; UGT1A7 [UDP glucuronosyltransferase 1 family, polypeptide A7]; UGT8 [UDP glycosyltransferase 8]; UIMC1 [ubiquitin interaction motif containing 1]; ULBP1 [UL16 binding protein 1]; ULK2 [unc-51-like kinase 2 (C. elegans)]; UMOD [uromodulin]; UMP [uridine monophosphate synthetase]; UNC13D [unc-13 homolog D (C. elegans)]; UNC93B1 [unc-93 homolog B1 (C. elegans)]; UNG [uracil-DNA glycosylase]; UQCRFS1 [ubiquinol-cytochrome c reductase, Rieske iron-sulfur protein 1]; UROD [uroporphyrigen decarboxylase]; USF1 [upstream transcription factor 1]; USF2 [upstream transcription factor 2; c-fos interacting]; USP18 [ubiquitin specific peptidase 18]; USP34 [ubiquitin specific peptidase 34]; UTRN [urophilin]; UTS2 [urotensin 2]; VAMP8 [vesicle-associated membrane protein 8 (endobrevin)]; VAPA [VAMP (vesicle-associated membrane protein)-associated protein A, 33 kDa]; VASP [vasodilator-stimulated phosphoprotein]; VAV1 [vav 1 guanine nucleotide exchange factor]; VAV3 [vav 3 guanine nucleotide exchange factor]; VCA1M [vascular cell adhesion molecule 1]; VCAN [versican]; VCL [vinculin]; VDAC1 [voltage-dependent anion channel 1]; VDR [vitamin D (1-25-dihydroxyvitamin D3) receptor]; VEGFA [vascular endothelial growth factor A]; VEGFC [vascular endothelial growth factor C]; VHL [von Hippel-Lindau tumor suppressor]; VIM [vimentin]; VIP [vasoactive intestinal peptide]; VIPR1 [vasoactive intestinal peptide receptor 1]; VIPR2 [vasoactive intestinal peptide receptor 2]; VLDLR [very low density lipoprotein receptor]; VMA1 [vimentin-type intermediate filament associated coiled-coil protein]; VPREB1 [pre-B lymphocyte 1]; VPS39 [vacuolar protein sorting 39 homolog (S. cerevisiae)]; VTN [vitronectin]; VWF [von Willebrand factor]; WARS [tryptophanyl-tRNA synthetase]; WAS [Wiskott-Aldrich syndrome (eczema-thrombocytopenia)]; WASF1 [WAS protein family, member 1]; WASF2 [WAS protein family, member 2]; WASL [Wiskott-Aldrich syndrome-like]; WDFY3 [WD repeat and FYVE domain containing 3]; WDR36 [WD repeat domain 36]; WEE1 [WEE1 homolog (S. pombe)]; WIP1 [WNT inhibitory factor 1]; WIPF1 [WAS/WASL interacting protein family, member 1]; WNK1 [WNK lysine deficient protein kinase 1]; WNT5A [wntless-type MMTV integration site family, member 5A]; WRN [ Werner syndrome, RecQ helicase-like]; WT1 [Wilms tumor 1]; XBP1 [X-box binding protein 1]; XCL1 [chemokine (C motif) ligand 1]; XDH [xanthine dehydrogenase]; XLAP [X-linked inhibitor of apoptosis]; XPA [xeroderma pigmentosum, complementation group A]; XPC [xeroderma pigmentosum, complementation group C]; XPO5 [exportin 5]; XRCC1 [X-ray repair complementing defective repair in Chinese hamster cells 1]; XRCC2 [X-ray repair complementing defective repair in Chinese hamster cells 2]; XRCC3 [X-ray repair complementing defective repair in Chinese hamster cells 3]; XRCC4 [X-ray repair complementing defective repair in Chinese hamster cells 4]; XRCC5 [X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand break-rejoining)]; XRCC6 [X-ray repair complementing defective repair in Chinese hamster cells 6]; YAP1 [Yes-associated protein 1]; YARS [tyrosyl-tRNA synthetase]; YBX1 [Y box binding protein 1]; YES1 [yes-1 Yamaguchi sarcoma viral oncogene homolog 1]; YPEL1 [yppee-like 1 (Drosophila)]; YPEL2 [yppee-like 2 (Drosophila)]; YWHAB [tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide]; YWHAAQ [tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide]; YWHAX [tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide]; YY1 [YY1 transcription factor]; ZAP70 [zeta-chain (TCR) associated protein kinase 70 kDa]; ZBED1 [zinc finger, BED-type containing 1]; ZC3H12A [zinc finger CCCH-type containing 12A]; ZC3H12D [zinc finger CCCH-type containing 12D]; ZFR [zinc finger RNA binding protein]; ZNF148 [zinc finger protein 148]; ZNF267 [zinc finger protein 267]; ZNF287 [zinc finger protein 287]; ZNF300 [zinc finger protein 300]
The immunodeficiency proteins are typically selected based on an experimental association of the immunodeficiency protein to an animal disease or condition, especially a mammalian, e.g., a human disease or condition. For example, the expression of an immunodeficiency protein in a particular tissue may be elevated or depressed in a population having an immunodeficiency disease or condition relative to a population lacking the disease or condition. Differences in protein levels may be assessed using proteomic techniques including but not limited to Western blot, immunohistochemical staining, enzyme linked immunosorbent assay (ELISA), and mass spectrometry. Alternatively, the immunodeficiency proteins may be identified by obtaining gene expression profiles of the genes encoding the proteins using genomic techniques including but not limited to DNA microarray analysis, serial analysis of gene expression (SAGE), and quantitative real-time polymerase chain reaction (Q-PCR).

Exemplary immunodeficiency proteins are those encoded by RAG1, RAG2, FOXL1 or DNAPK. Most known human immunodeficiency genes have a recognized mouse ortholog. It should be understood that the gene designations as used herein, while referring to the human and mouse genomes, encompass the close homologs of any of these that have been identified among other animals including other mammals, including but not limited to rats, hamsters, cats, and dogs. Close homologs can be identified by sequence analysis, phylogenetic analysis, functional assays, or any combination thereof.

(i) RAG1

The RAG1 gene (also known as recombination activating gene 1, RAG-1, RNF741, v(DJ) recombination-activating protein and recombination activating protein) is involved in activation of immunoglobulin V-D-J recombination. The encoded protein is involved in recognition of the DNA substrate, but stable binding and cleavage activity also requires RAG2. Defects in RAG1 are implicated in the cause of several immunodeficiency diseases including certain forms of Severe Combined Immunodeficiency.

(ii) RAG2

The RAG2 gene (also known as recombination activating gene 2, RAG-2, and V(DJ) recombination-activating protein 2), encodes a protein that is involved in the initiation of V(DJ) recombination during B and T cell development. The encoded protein forms a complex with the product of RAG1 and the complex is capable of making double-strand breaks in DNA at specific recombination signal sequences. RAG1 is believed to contain most of the catalytic activity, while the N-terminal of RAG2 is thought to form structure that provides a binding scaffold for tight binding of the complex to DNA. Mutations in RAG2 cause Omenn syndrome, a form of severe combined immunodeficiency associated with autoimmune-like symptoms.

(iii) DNAPK (PRKDC)

The DNAPK gene (also known as DNAPK1, PRKDC, DNA-PKcs, HYRC and p5300) encodes the catalytic subunit of a nuclear DNA-dependent serine/threonine protein kinase (DNA-PK). The second component is the autoimmune antigen Ku (MIM 152690), which is encoded by the G22P1 gene on chromosome 22q. On its own, the catalytic subunit of DNA-PK is inactive and relies on the G22P1 component to direct it to the DNA and trigger its kinase activity; PRKDC must be bound to DNA to express its catalytic properties. DNAPK has been shown to interact with NCOA6, CHEK1, Werner syndrome ATP-dependent helicase, RPA2, ILF3, DCLRE1C, ILF2, Ataxia telangiectasia mutated, Ku80, CDC5L, P53, CIB1, C1D and CHUK.

Animals

The term "animal," as used herein, refers to a non-human animal. The animal may be an embryo, a juvenile, or an adult. Suitable animals include vertebrates such as mammals, birds, reptiles, amphibians, and fish. Examples of suitable mammals include without limit rodents, companion ani-
mals, livestock, and primates. Non-limiting examples of rodents include mice, rats, hamsters, gerbils, and guinea pigs. Suitable companion animals include but are not limited to cats, dogs, rabbits, hedgehogs, and ferrets. Non-limiting examples of livestock include horses, goats, sheep, swine, cattle, llamas, and alpacas. Suitable primates include but are not limited to capuchin monkeys, chimpanzees, lemurs, macaques, marmosets, tamarins, spider monkeys, squirrel monkeys, and vervet monkeys. Non-limiting examples of birds include chickens, turkeys, ducks, and geese. Alternatively, the animal may be an invertebrate such as an insect, a nematode, and the like. Non-limiting examples of insects include Drosophila and mosquitoes. An exemplary animal is a rat. Non-limiting examples of suitable rat strains include Dahl Salt-Sensitive, Fischer 344, Lewis, Long Evans Hooded, Sprague-Dawley, and Wistar. In another iteration of the invention, the animal does not comprise a genetically modified mouse. In each of the foregoing iterations of suitable animals for the invention, the animal does not include exogenously introduced, randomly integrated transposon sequences.

The immunodeficiency protein may be from any of the animals listed above. Furthermore, the immunodeficiency protein may be a human immunodeficiency protein. Additionally, the immunodeficiency protein may be a bacterial or fungal immunodeficiency protein. The type of animal and the source of the protein can and will vary. The protein may be endogenous or exogenous (such as an orthologous protein). As an example, the genetically modified animal may be a rat, cat, dog, or pig, and the orthologous immunodeficiency protein may be human. Alternatively, the genetically modified animal may be a rat, cat, or pig, and the orthologous immunodeficiency protein may be canine. One of skill in the art will readily appreciate that numerous combinations are possible.

Additionally, the immunodeficiency-related gene may be modified to include a tag or reporter gene as are well-known. Reporter genes include those encoding selectable markers such as chloramphenicol acetyltransferase (CAT) and neomycin phosphotransferase (neo), and those encoding a fluorescent protein such as green fluorescent protein (GFP), red fluorescent protein, or any genetically engineered variant thereof that improves the reporter performance. Non-limiting examples of known such FP variants include EGFp, blue fluorescent protein (EBFP, EBFP2, Azurite, mKalanma1), cyan fluorescent protein (ECFP, Cerulean, CyPet) and yellow fluorescent protein derivatives (YFP, Citrine, Venus, YPet). For example, in a genetic construct containing a reporter gene, the reporter gene sequence can be fused directly to the targeted gene to create a gene fusion. A reporter sequence can be integrated in a targeted manner in the targeted gene, for example the reporter sequences may be integrated specifically at the 5' or 3' end of the targeted gene. The two genes are thus under the control of the same promoter elements and are transcribed into a single messenger RNA molecule. Alternatively, the reporter gene may be used to monitor the activity of a promoter in a genetic construct, for example by placing the reporter sequence downstream of the target promoter such that expression of the reporter gene is under the control of the target promoter, and activity of the reporter gene can be directly and quantitatively measured, typically in comparison to activity observed under a strong consensus promoter. It will be understood that doing so may or may not lead to destruction of the targeted gene.

(III) Zinc Finger-Mediated Genome Editing

Generally, the genetically modified animal or cell detailed above in sections (I) and (II), respectively, is generated using a zinc finger nuclease-mediated genome editing process. The process for editing a chromosomal sequence comprises: (a) introducing into an embryo or cell at least one nucleic acid encoding a zinc finger nuclease that recognizes a target sequence in the chromosomal sequence and is able to cleave a site in the chromosomal sequence, and optionally, (i) at least one donor polynucleotide comprising a sequence for integration flanked by an upstream sequence and a downstream sequence that share substantial sequence identity with either side of the cleavage site, or (ii) at least one exchange polynucleotide comprising a sequence that is substantially identical to a portion of the chromosomal sequence at the cleavage site and which further comprises at least one nucleotide change; and (b) culturing the embryo or cell to allow
expression of the zinc finger nuclease such that the zinc finger nuclease introduces a double-stranded break into the chromosomal sequence, and wherein the double-stranded break is repaired by (i) a non-homologous end-joining repair process such that an inactivating mutation is introduced into the chromosomal sequence, or (ii) a homology-directed repair process such that the sequence in the donor polynucleotide is integrated into the chromosomal sequence or the sequence in the exchange polynucleotide is exchanged with the portion of the chromosomal sequence.

[0051] Components of the zinc finger nuclease-mediated method are described in more detail below.

(a) Zinc Finger Nuclease

[0052] The method comprises, in part, introducing into an embryo or cell at least one nucleic acid encoding a zinc finger nuclease. Typically, a zinc finger nuclease comprises a DNA binding domain (i.e., zinc finger) and a cleavage domain (i.e., nuclease). The DNA binding and cleavage domains are described below. The nucleic acid encoding a zinc finger nuclease may comprise DNA or RNA. For example, the nucleic acid encoding a zinc finger nuclease may comprise mRNA. When the nucleic acid encoding a zinc finger nuclease comprises mRNA, the mRNA molecule may be 5’ capped. Similarly, when the nucleic acid encoding a zinc finger nuclease comprises mRNA, the mRNA molecule may be polyadenylated. An exemplary nucleic acid according to the method is a capped and polyadenylated mRNA molecule encoding a zinc finger nuclease. Methods for capping and polyadenylating mRNA are known in the art.

[0053] (i) Zinc Finger Binding Domain

[0054] Zinc finger binding domains may be engineered to bind and to any nucleic acid sequence of choice. See, for example, Beerli et al. (2002) Nat. Biotechnol. 20:135-141; Pabo et al. (2001) Ann. Rev. Biochem. 70:313-340; Isalan et al. (2001) Nat. Biotechnol. 19:656-660; Segal et al. (2001) Curr. Opin. Biotechnol. 12:632-637; Choo et al. (2000) Curr. Opin. Struct. Biol. 10:411-416; Zhang et al. (2000) J. Biol. Chem. 275(43):33850-33860; Doyon et al. (2008) Nat. Biotechnol. 26:702-708; and Santiago et al. (2008) Proc. Natl. Acad. Sci. USA 105:5809-5814. An engineered zinc finger binding domain may have a novel binding specificity compared to a naturally-occurring zinc finger protein. Engineering methods include, but are not limited to, rational design and various types of selection. Rational design includes, for example, using databases comprising doublet, triplet, and/or quadruplet nucleotide sequences and individual zinc finger amino acid sequences, in which each doublet, triplet or quadruplet nucleotide sequence is associated with one or more amino acid sequences of zinc fingers which bind the particular triplet or quadruplet sequence. See, for example, U.S. Pat. Nos. 6,453,242 and 6,534,261, the disclosures of which are incorporated by reference herein in their entirety. As an example, the algorithm of described in U.S. Pat. No. 6,453,242 may be used to design a zinc finger binding domain to target a preselected sequence. Alternative methods, such as rational design using a nondegenerate recognition code table may also be used to design a zinc finger binding domain to target a specific sequence (Sern et al. (2002) Biochemistry 41:7074-7081). Publically available web-based tools for identifying potential target sites in DNA sequences and designing zinc finger binding domains may be found at http://www.zincfingertools.org and http://bind.gdb.iastate.edu/ZiFiT/, respectively (Mandell et al. (2006) Nuc. Acid Res. 34:W516-W523; Sander et al. (2007) Nuc. Acid Res. 35:W599-W605).

[0055] A zinc finger binding domain may be designed to recognize a DNA sequence ranging from about 3 nucleotides to about 21 nucleotides in length, or from about 8 to about 19 nucleotides in length. In general, the zinc finger binding domains of the zinc finger nucleases disclosed herein comprise at least three zinc finger recognition regions (i.e., zinc fingers). In one embodiment, the zinc finger binding domain may comprise four zinc finger recognition regions. In another embodiment, the zinc finger binding domain may comprise five zinc finger recognition regions. In still another embodiment, the zinc finger binding domain may comprise six zinc finger recognition regions. A zinc finger binding domain may be designed to bind to any suitable target DNA sequence. See, for example, U.S. Pat. Nos. 6,607,882; 6,534,261 and 6,453,242, the disclosures of which are incorporated by reference herein in their entirety.

[0056] Exemplary methods of selecting a zinc finger recognition region may include phage display and two-hybrid systems, and are disclosed in U.S. Pat. Nos. 5,789,538; 5,925,523; 6,007,988; 6,013,453; 6,410,248; 6,140,466; 6,200,759; and 6,242,568; as well as WO 98/37186; WO 98/53057; WO 00/27878; WO 01/88197 and GB 2,338,237, each of which is incorporated by reference herein in its entirety. In addition, enhancement of binding specificity for zinc finger binding domains has been described, for example, in WO 02/077227.

[0057] Zinc finger binding domains and methods for design and construction of fusion proteins (and polynucleotides encoding same) are known to those of skill in the art and are described in detail in U.S. Patent Application Publication Nos. 20050064474 and 20060188987, each incorporated by reference herein in its entirety. Zinc finger recognition regions and/or multi-fingered zinc finger proteins may be linked together using suitable linker sequences, including for example, linkers of five or more amino acids in length. See, U.S. Pat. Nos. 6,479,626; 6,903,185; and 7,153,949, the disclosures of which are incorporated by reference herein in their entirety, for non-limiting examples of linker sequences of six or more amino acids in length. The zinc finger binding domain described herein may include a combination of suitable linkers between the individual zinc fingers of the protein.

[0058] In some embodiments, the zinc finger nuclease may further comprise a nuclear localization signal or sequence (NLS). A NLS is an amino acid sequence which facilitates targeting the zinc finger nuclease protein into the nucleus to introduce a double stranded break at the target sequence in the chromosome. Nuclear localization signals are known in the art. See, for example, Makkerr et al. (1996) Current Biology 6:1025-1027.

[0059] An exemplary zinc finger DNA binding domain recognizes and binds a sequence having at least about 80% sequence identity to a sequence chosen from SEQ ID NOS: 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 (listed in the Examples herein below). In other embodiments, the sequence identity with any chosen sequence may be about 88%, 82%, 85%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

[0060] (ii) Cleavage Domain

[0061] A zinc finger nuclease also includes a cleavage domain. The cleavage domain portion of the zinc finger nucleases disclosed herein may be obtained from any endonuclease or exonuclease. Non-limiting examples of endonu-
cleases from which a cleavage domain may be derived include, but are not limited to, restriction endonucleases and homing endonucleases. See, for example, 2002-2003 Catalog, New England Biolabs, Beverly, Mass.; and Belfort et al. (1997) Nucleic Acids Res. 25:3379-3388 or www.neb.com. Additional enzymes that cleave DNA are known (e.g., S1 Nuclease; mung bean nuclease; pancreatic DNase 1; micrococcal nuclease; yeast HO endonuclease). See also Linn et al. (eds.) Nucleases, Cold Spring Harbor Laboratory Press, 1993. One or more of these enzymes (or functional fragments thereof) may be used as a source of cleavage domains.

A cleavage domain also may be derived from an enzyme or portion thereof, as described above, that requires dimerization for cleavage activity. Two zinc finger nucleases may be required for cleavage, as each nuclease comprises a monomer of the active enzyme dimer. Alternatively, a single zinc finger nuclease may comprise both monomers to create an active enzyme dimer. As used herein, an “active enzyme dimer” is an enzyme dimer capable of cleaving a nucleic acid molecule. The two cleavage monomers may be derived from the same endonuclease (or functional fragments thereof), or each monomer may be derived from a different endonuclease (or functional fragments thereof).

When two cleavage monomers are used to form an active enzyme dimer, the recognition sites for the two zinc finger nucleases are preferably disposed such that binding of the two zinc finger nucleases to their respective recognition sites places the cleavage monomers in a spatial orientation to each other that allows the cleavage monomers to form an active enzyme dimer, e.g., by dimerizing. As a result, the near edges of the recognition sites may be separated by about 5 to about 18 nucleotides. For instance, the near edges may be separated by about 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18 nucleotides. It will however be understood that any integral number of nucleotides or nucleotide pairs may intervene between two recognition sites (e.g., from about 2 to about 50 nucleotide pairs or more). The near edges of the recognition sites of the zinc finger nucleases, such as for example those described in detail herein, may be separated by 6 nucleotides. In general, the site of cleavage lies between the recognition sites.

Restriction endonucleases (restriction enzymes) are present in many species and are capable of sequence-specific binding to DNA (at a recognition site), and cleaving DNA at or near the site of binding. Certain restriction enzymes (e.g., Type IIS) cleave DNA at sites removed from the recognition site and have separable binding and cleavage domains. For example, the Type IIS enzyme Fok I catalyzes double-stranded cleavage of DNA at 9 nucleotides from its recognition site on one strand and 13 nucleotides from its recognition site on the other. See, for example, U.S. Pat. Nos. 5,356,802; 5,436,150 and 5,487,994; as well as Li et al. (1992) Proc. Natl. Acad. Sci. USA 89:4275-4279; Li et al. (1993) Proc. Natl. Acad. Sci. USA 90:2764-2768; Kim et al. (1994a) Proc. Natl. Acad. Sci. USA 91:883-887; Kim et al. (1994b) J. Biol. Chem. 269:31, 978-31, 982. Thus, a zinc finger nuclease may comprise the cleavage domain from at least one Type IIS restriction enzyme and one or more zinc finger binding domains, which may or may not be engineered. Exemplary Type IIS restriction enzymes are described for example in International Publication WO 07/014,275, the disclosure of which is incorporated by reference herein in its entirety. Additional restriction enzymes also contain separable binding and cleavage domains, and these also are contemplated by the present disclosure. See, for example, Roberts et al. (2003) Nucleic Acids Res. 31:418-420.

An exemplary Type IIS restriction enzyme, whose cleavage domain is separable from the binding domain, is Fok I. This particular enzyme is active as a dimer (Bitinaite et al. (1998) Proc. Natl. Acad. Sci. USA 95: 10, 570-10, 575). Accordingly, for the purposes of the present disclosure, the portion of the Fok I enzyme used in a zinc finger nuclease is considered a cleavage monomer. Thus, for targeted double-stranded cleavage using a Fok I cleavage domain, two zinc finger nucleases, each comprising a Fok I cleavage monomer, may be used to reconstitute an active enzyme dimer. Alternatively, a single polypeptide molecule containing a zinc finger binding domain and two Fok I cleavage monomers may also be used.

In certain embodiments, the cleavage domain may comprise one or more engineered cleavage monomers that minimize or prevent homodimerization, as described, for example, in U.S. Patent Publication 20050064474, 20060188987, and 20080131962, each of which is incorporated by reference herein in its entirety. By way of non-limiting example, amino acid residues at positions 446, 447, 479, 483, 484, 486, 487, 490, 491, 496, 498, 499, 500, 531, 534, 537, and 538 of Fok I are all targets for influencing dimerization of the Fok I cleavage half-domains. Exemplary engineered cleavage monomers of Fok I that form obligate heterodimers include a pair in which a first cleavage monomer includes mutations at amino acid residue positions 490 and 538 of Fok I and a second cleavage monomer that includes mutations at amino acid residue positions 486 and 499.

Thus, in one embodiment, a mutation at amino acid position 490 replaces Gln (G) with Lys (K); a mutation at amino acid residue 538 replaces Ile (I) with Lys (K); a mutation at amino acid residue 486 replaces Gln (Q) with Glu (E); and a mutation at position 499 replaces Ile (I) with Lys (K). Specifically, the engineered cleavage monomers may be prepared by mutating positions 490 from E to K and 538 from I to K in one cleavage monomer to produce an engineered cleavage monomer designated “E490K:1538K” and by mutating positions 486 from Q to E and 499 from I to K in another cleavage monomer to produce an engineered cleavage monomer designated “Q486E:1499L.” The above described engineered cleavage monomers are obligate heterodimer mutants in which aberrant cleavage is minimized or abolished. Engineered cleavage monomers may be prepared using a suitable method, for example, by site-directed mutagenesis of wild-type cleavage monomers (Fok I) as described in U.S. Patent Publication No. 20050064474 (see Example 5).

The zinc finger nuclease described above may be engineered to introduce a double stranded break at the targeted site of integration. The double stranded break may be at the targeted site of integration, or it may be up to 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, or 1000 nucleotides away from the site of integration. In some embodiments, the double stranded break may be up to 1, 2, 3, 4, 5, 10, 15, or 20 nucleotides away from the site of integration. In other embodiments, the double stranded break may be up to 10, 15, 20, 25, 30, 35, 40, 45, or 50 nucleotides away from the site of integration. In yet other embodiments, the double stranded break may be up to 50, 100, or 1000 nucleotides away from the site of integration.

(b) Optional Donor Polynucleotide

The method for editing chromosomal sequences encoding immunodeficiency proteins may further comprise
introducing at least one donor polynucleotide comprising a sequence encoding an immunodeficiency protein into the embryo or cell. A donor polynucleotide comprises at least three components: the sequence coding the immunodeficiency protein, an upstream sequence, and a downstream sequence. The sequence encoding the protein is flanked by the upstream and downstream sequence, wherein the upstream and downstream sequences share sequence similarity with either side of the site of integration in the chromosome.

Typically, the donor polynucleotide will be DNA. The donor polynucleotide may be a DNA plasmid, a bacterial artificial chromosome (BAC), a yeast artificial chromosome (YAC), a viral vector, a linear piece of DNA, a PCR fragment, a naked nucleic acid, or a nucleic acid complexed with a delivery vehicle such as a liposome or poloxamer. An exemplary donor polynucleotide comprising the sequence encoding an immunodeficiency protein may be a BAC.

The sequence of the donor polynucleotide that encodes the immunodeficiency protein may include coding (i.e., exon) sequence, as well as intron sequences and upstream regulatory sequences (such as, e.g., a promoter). Depending upon the identity and the source of the immunodeficiency protein, the size of the sequence encoding the immunodeficiency protein can and will vary. For example, the sequence encoding the immunodeficiency protein may range in size from about 1 kb to about 5,000 kb.

The donor polynucleotide also comprises upstream and downstream sequences flanking the sequence encoding the immunodeficiency protein. The upstream and downstream sequences in the donor polynucleotide are selected to promote recombination between the chromosomal sequence of interest and the donor polynucleotide. The upstream sequence, as used herein, refers to a nucleic acid sequence that shares sequence similarity with the chromosomal sequence upstream of the targeted site of integration. Similarly, the downstream sequence refers to a nucleic acid sequence that shares sequence similarity with the chromosomal sequence downstream of the targeted site of integration. The upstream and downstream sequences in the donor polynucleotide may share about 75%, 80%, 85%, 90%, 95%, or 100% sequence identity with the targeted chromosomal sequence. In other embodiments, the upstream and downstream sequences in the donor polynucleotide may share about 95%, 96%, 97%, 98%, 99%, or 100% sequence identity with the targeted chromosomal sequence. In an exemplary embodiment, the upstream and downstream sequences in the donor polynucleotide may share about 99% or 100% sequence identity with the targeted chromosomal sequence.

An upstream or downstream sequence may comprise from about 50 bp to about 2500 bp. In one embodiment, an upstream or downstream sequence may comprise about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, or 2500 bp. An exemplary upstream or downstream sequence may comprise about 200 bp to about 2000 bp, about 600 bp to about 1000 bp, or more particularly about 700 bp to about 1000 bp.

In some embodiments, the donor polynucleotide may further comprise a marker. Such a marker may make it easy to screen for targeted integrations. Non-limiting examples of suitable markers include restriction sites, fluorescent proteins, or selectable markers.

One of skill in the art would be able to construct a donor polynucleotide as described herein using well-known standard recombinant techniques (see, for example, Sambrook et al., 2001 and Ausubel et al., 1996).

In the method detailed above for integrating a sequence encoding the immunodeficiency protein, a double stranded break introduced into the chromosomal sequence by the zinc finger nuclease is repaired, via homologous recombination with the donor polynucleotide, such that the sequence encoding the immunodeficiency protein is integrated into the chromosome. The presence of a double-stranded break facilitates integration of the sequence into the chromosome. A donor polynucleotide may be physically integrated or, alternatively, the donor polynucleotide may be used as a template for repair of the break, resulting in the introduction of the sequence encoding the immunodeficiency protein as well as all or part of the upstream and downstream sequences of the donor polynucleotide into the chromosome. Thus, endogenous chromosomal sequence may be converted to the sequence of the donor polynucleotide.

(c) Optional Exchange Polynucleotide

The method for editing chromosomal sequences encoding immunodeficiency protein may further comprise introducing into the embryo or cell at least one exchange polynucleotide comprising a sequence that is substantially identical to the chromosomal sequence at the site of cleavage and which further comprises at least one specific nucleotide change.

Typically, the exchange polynucleotide will be DNA. The exchange polynucleotide may be a DNA plasmid, a bacterial artificial chromosome (BAC), a yeast artificial chromosome (YAC), a viral vector, a linear piece of DNA, a PCR fragment, a naked nucleic acid, or a nucleic acid complexed with a delivery vehicle such as a liposome or poloxamer. An exemplary exchange polynucleotide may be a DNA plasmid.

The sequence in the exchange polynucleotide is substantially identical to a portion of the chromosomal sequence at the site of cleavage. In general, the sequence of the exchange polynucleotide will share enough sequence identity with the chromosomal sequence such that the two sequences may be exchanged by homologous recombination. For example, the sequence in the exchange polynucleotide may have at least about 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity with a portion of the chromosomal sequence.

Importantly, the sequence in the exchange polynucleotide comprises at least one specific nucleotide change with respect to the sequence of the corresponding chromosomal sequence. For example, one nucleotide in a specific codon may be changed to another nucleotide such that the codon codes for a different amino acid. In one embodiment, the sequence in the exchange polynucleotide may comprise one specific nucleotide change such that the encoded protein comprises one amino acid change. In other embodiments, the sequence in the exchange polynucleotide may comprise two, three, four, or more specific nucleotide changes such that the encoded protein comprises one amino acid change. In still other embodiments, the sequence in the exchange polynucleotide may comprise three nucleotide deletions or insertions such that the reading frame of the coding reading is not altered (and a functional protein is...
produced). The expressed protein, however, would comprise a single amino acid deletion or insertion.

The length of the sequence in the exchange polynucleotide that is substantially identical to a portion of the chromosomal sequence at the site of cleavage can and will vary. In general, the sequence in the exchange polynucleotide may range from about 50 by to about 10,000 by in length. In various embodiments, the sequence in the exchange polynucleotide may be about 100, 200, 400, 600, 800, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3200, 3400, 3600, 3800, 4000, 4200, 4400, 4600, 4800, or 5000 by in length. In other embodiments, the sequence in the exchange polynucleotide may be about 5500, 6000, 6500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, or 10,000 by in length.

One of skill in the art would be able to construct an exchange polynucleotide as described herein using well-known standard recombinant techniques (see, for example, Sambrook et al., 2001 and Ausubel et al., 1996).

In the method detailed above for modifying a chromosomal sequence, a double stranded break introduced into the chromosomal sequence by the zinc finger nuclease is repaired, via homologous recombination with the exchange polynucleotide, such that the sequence in the exchange polynucleotide may be exchanged with a portion of the chromosomal sequence. The presence of the double stranded break facilitates homologous recombination and repair of the break. The exchange polynucleotide may be physically integrated or, alternatively, the exchange polynucleotide may be used as a template for repair of the break, resulting in the exchange of the sequence information in the exchange polynucleotide with the sequence information in that portion of the chromosomal sequence. Thus, a portion of the endogenous chromosomal sequence may be converted to the sequence of the exchange polynucleotide. The changed nucleotide(s) may be at or near the site of cleavage. Alternatively, the changed nucleotide(s) may be anywhere in the exchanged sequences. As a consequence of the exchange, however, the chromosomal sequence is modified.

(d) Delivery of Nucleic Acids

To mediate zinc finger nuclease genomic editing, at least one nucleic acid molecule encoding a zinc finger nuclease and, optionally, at least one other polynucleotide or at least one donor polynucleotide are delivered to the embryo or the cell of interest. Typically, the embryo is a fertilized one-cell stage embryo of the species of interest.

Suitable methods of introducing the nucleic acids to the embryo or cell include microinjection, electroporation, sonoporation, biolistics, calcium phosphate-mediated transfection, cationic transfection, liposome transfection, dextrimer transfection, heat shock transfection, nucleofection transfection, magnetofection, lipofection, lipofection, lipofection, optical transfection, proprietary agent-enhanced uptake of nucleic acids, and delivery via liposomes, immunoliposomes, virosomes, or artificial virions. In one embodiment, the nucleic acids may be introduced into an embryo by microinjection. The nucleic acids may be microinjected into the nucleus or the cytoplasm of the embryo. In another embodiment, the nucleic acids may be introduced into a cell by nucleofection.

In embodiments in which both a nucleic acid encoding a zinc finger nuclease and a donor (or exchange) polynucleotide are introduced into an embryo or cell, the ratio of donor (or exchange) polynucleotide to nucleic acid encoding a zinc finger nuclease may range from about 1:10 to about 10:1. In various embodiments, the ratio of donor (or exchange) polynucleotide to nucleic acid encoding a zinc finger nuclease may range from about 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In one embodiment, the ratio may be about 1:1.

In embodiments in which more than one nucleic acid encoding a zinc finger nuclease and, optionally, more than one donor (or exchange) polynucleotide are introduced into an embryo or cell, the nucleic acids may be introduced simultaneously or sequentially. For example, nucleic acids encoding the zinc finger nucleases, each specific for a distinct recognition sequence, as well as the optional donor (or exchange) polynucleotides, may be introduced at the same time. Alternatively, each nucleic acid encoding a zinc finger nuclease, as well as the optional donor (or exchange) polynucleotides, may be introduced sequentially.

(e) Culturing the Embryo or Cell

The method of inducing genomic editing with a zinc finger nuclease further comprises culturing the embryo or cell comprising the introduced nucleic acid(s) to allow expression of the zinc finger nuclease. An embryo may be cultured in vitro (e.g., in cell culture). Typically, the embryo is cultured at an appropriate temperature and in appropriate media with the necessary O2/CO2 ratio to allow the expression of the zinc finger nuclease. Suitable non-limiting examples of media include M2, M16, KSOM, BMOC, and HTF media. A skilled artisan will appreciate that culture conditions can and will vary depending on the species of embryo. Routine optimization may be used, in all cases, to determine the best culture conditions for a particular species of embryo. In some cases, a cell line may be derived from an in vitro-cultured embryo (e.g., an embryonic stem cell line).

Alternatively, an embryo may be cultured in vivo by transferring the embryo into the uterus of a female host. Generally speaking, the female host is from the same or similar species as the embryo. Preferably, the female host is pseudo-pregnant. Methods of preparing pseudo-pregnant female hosts are known in the art. Additionally, methods of transferring an embryo into a female host are known. Culturing an embryo in vivo permits the embryo to develop and may result in a live birth of an animal derived from the embryo. Such an animal would comprise the edited chromosomal sequence encoding the immunodeficiency protein in every cell of the body.

Similarly, cells comprising the introduced nucleic acids may be cultured using standard procedures to allow expression of the zinc finger nuclease. Standard cell culture techniques are described, for example, in Santiago et al. (2008) PNAS105:5809-5814; Moehle et al. (2007) PNAS104:3055-3060; Umem et al. (2005) Nature 435:646-651; and Lombardo et al. (2007) Nat. Biotechnology 25:1298-1306. Those of skill in the art appreciate that methods for culturing cells are known in the art and can and will vary depending on the cell type. Routine optimization may be used, in all cases, to determine the best techniques for a particular cell type.

Upon expression of the zinc finger nuclease, the chromosomal sequence may be edited. In cases in which the cell comprises an expressed zinc finger nuclease but no donor (or exchange) polynucleotide, the zinc finger nuclease recognizes, binds, and cleaves the target sequence in
the chromosomal sequence of interest. The double-stranded break introduced by the zinc finger nuclease is repaired by an error-prone non-homologous end-joining DNA repair process. Consequently, a deletion, insertion, or nonsense mutation may be introduced in the chromosomal sequence such that the sequence is inactivated.

[0092] In cases in which the embryo or cell comprises an expressed zinc finger nuclease as well as a donor (or exchange) polynucleotide, the zinc finger nucleosome recognizes, binds, and cleaves the target sequence in the chromosome. The double-stranded break introduced by the zinc finger nuclease is repaired, via homologous recombination with the donor (or exchange) polynucleotide, such that the sequence in the donor polynucleotide is integrated into the chromosomal sequence (or a portion of the chromosomal sequence is converted to the sequence in the exchange polynucleotide). As a consequence, a sequence may be integrated into the chromosomal sequence (or a portion of the chromosomal sequence may be modified).

[0093] The genetically modified animals disclosed herein may be crossbred to create animals comprising more than one edited chromosomal sequence or to create animals that are homozygous for one or more edited chromosomal sequences. For example, two animals comprising the same edited chromosomal sequence may be crossbred to create an animal homozygous for the edited chromosomal sequence. Alternatively, animals with different edited chromosomal sequences may be crossbred to create an animal comprising both edited chromosomal sequences.

[0094] For example, animal A comprising an inactivated Rag2 chromosomal sequence may be crossbred with animal B comprising a chromosomally integrated sequence encoding a human RAG2 protein to give rise to a “humanized” RAG2 offspring comprising both the inactivated Rag2 chromosomal sequence and the chromosomally integrated human RAG2 sequence. Similarly, an animal comprising an inactivated DNAPK chromosomal sequence may be crossbred with an animal comprising a chromosomally integrated sequence encoding the human DNAPK protein to generate “humanized” DNAPK offspring. Moreover, a humanized FOXN1 animal may be crossbred with a humanized DNAPK animal to create a humanized FOXN1/DNAPK. Those of skill in the art will appreciate that many combinations are possible. Exemplary combinations are presented above, in Table A.

[0095] In other embodiments, an animal comprising an edited chromosomal sequence disclosed herein may be crossbred to combine the edited chromosomal sequence with other genetic backgrounds. By way of non-limiting example, other genetic backgrounds may include wild-type genetic backgrounds, genetic backgrounds with deletion mutations, genetic backgrounds with another targeted integration, and genetic backgrounds with non-targeted integrations. Suitable integrations may include without limit nucleic acids encoding drug transporter proteins, Mdr protein, and the like.

(IV) Applications

[0096] A further aspect of the present disclosure encompasses a method for assessing at least one effect of an agent. Suitable agents include without limit pharmaceutically active ingredients, drugs, food additives, pesticides, herbicides, toxins, industrial chemicals, household chemicals, and other environmental chemicals. For example, the effect of an agent may be measured in a “humanized” genetically modified animal, such that the information gained therefrom may be used to predict the effect of the agent in a human. In general, the method comprises contacting a genetically modified animal comprising at least one inactivated chromosomal sequence encoding an immunodeficiency protein and at least one chromosomally integrated sequence encoding an orthologous immunodeficiency protein with the agent, and comparing results of a selected parameter to results obtained from contacting a wild-type animal with the same agent. Selected parameters include but are not limited to (a) rate of elimination of the agent or its metabolite(s); (b) circulatory levels of the agent or its metabolite(s); (c) bioavailability of the agent or its metabolite(s); (d) rate of metabolism of the agent or its metabolite(s); (e) rate of clearance of the agent or its metabolite(s); (f) toxicity of the agent or its metabolite(s); (g) efficacy of the agent or its metabolite(s); (h) disposition of the agent or its metabolite(s); and (i) extrahepatic contribution to metabolic rate and clearance of the agent or its metabolite(s).

[0097] An additional aspect provides a method for assessing the therapeutic potential of an agent in an animal that may include contacting a genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein, and comparing results of a selected parameter to results obtained from a wild-type animal with no contact with the same agent. Selected parameters include but are not limited to a) spontaneous behaviors; b) performance during behavioral testing; c) physiological anomalies; d) abnormalities in tissues or cells; e) biochemical function; and f) molecular structures.

[0098] Also provided are methods to assess the effect(s) of an agent in an isolated cell comprising at least one edited chromosomal sequence encoding an immunodeficiency protein, as well as methods of assessing lysates of such cells (or cells derived from a genetically modified animal disclosed herein) to assess the effect(s) of an agent. For example, the role of a particular immunodeficiency protein in the metabolism of a particular agent may be determined using such methods. Similarly, substrate specificity and pharmacokinetic parameter may be readily determined using such methods. Those of skill in the art are familiar with suitable tests and/or procedures.

[0099] Yet another aspect encompasses a method for assessing the therapeutic efficacy of a potential gene therapy strategy. That is, a chromosomal sequence encoding an immunodeficiency-related protein may be modified such that the immunodeficiency effect is reduced or eliminated. In particular, the method comprises editing a chromosomal sequence encoding an immunodeficiency-related protein such that an altered protein product is produced.

[0100] Still yet another aspect encompasses a method of generating a cell line or cell lysate using a genetically modified animal comprising an edited chromosomal sequence encoding an immunodeficiency-related protein. An additional aspect encompasses a method of producing purified biological components using a genetically modified cell or animal comprising an edited chromosomal sequence encoding an immunodeficiency-related protein. Non-limiting examples of biological components include antibodies, cytokines, signal proteins, enzymes, receptor antagonists and receptor agonists.

[0101] It should be understood that the genetically modified animals, e.g., knockout and transgenic animals such as rats as described herein may include genes altered singly or in combination, including alteration to any one or more of Rag1,
Rag2, FoxN1, and DNAPK. Accordingly, for example, animals including a single, double or triple gene knock-out are contemplated. Any of these may be used in various methods in which alteration of one or more immunodeficiency genes may be useful. For example, genetically modified animals as described herein may be used in studies of hematopoietic cells, such as in the identification of progenitor cells including lymphoid progenitors and pluripotent stem cells; in the identification of new cytokines which play a role in the growth and differentiation of hematopoietic cells; in the analysis of the effect of known cytokines; and in the analysis of drugs effects on hematopoietic cells. Such animals can also be used in studies on pathogenetic mechanisms in disease caused by viral infections such as but not limited to influenza, West Nile virus, herpesviruses, picornaviruses, neurotropic coronavirus, Varicella-zoster (chicken pox), respiratory syncytial virus, cowpox, hepatitis B, rabies, and Dengue virus, and lymphotropic viruses including human immunodeficiency virus (HIV), human T lymphotropic virus (HTLV-1), and Epstein Barr virus (EBV), and also a virus that specifically infects rats but models the effects of a human-specific virus on its host, for example the rat-adapted influenza virus (see, e.g., H. Lebrec and G. R. Burleson (1994) Toxicology. July 1: 91(2):179-88).

[0102] Genetically modified animals may also be useful in methods for screening or evaluating new candidate therapeutic compounds or approaches, such as in screening of candidate therapeutic compounds for treating an immunodeficiency. Genetically modified animals may also be useful in studies of defense mechanisms against microorganisms that cause disease in immunocompromised patients such as cytomegalovirus, Pneumocystis carinii or Candida species. Genetically modified animals, such as for example knockout rats can be subjects for pre-clinical evaluation of a specific “gene therapy.” For example, genes may be introduced into hematopoietic progenitor cells, preferably into pluripotent stem cells with self-renewal capacity from patients with inherited genetic defects, or into pluripotent stem cells with self-renewal capacity from rat models of patients with inherited genetic defects, and the cells re-introduced into the genetically modified rats for the purpose of determining therapeutic usefulness of the modified cells. Genetically modified animals may also be useful for studying the biological mechanisms underlying immunodeficiency diseases and conditions caused by or linked to a mutation in an immunodeficiency gene such as Rag1, Rag2, FoxN1, or DNAPK.

[0103] Natural killer (NK) cells in nude rats are highly active compared to immunocompetent controls (see, e.g., N. Masu et al. Exp Anim. 2004 October; 53(5):399-407. PMID: 15516787), and NK cells participate in xenograft rejection and defend against carcinogenesis by killing tumor cells. A genetically modified animal as described herein, for example an animal in which an immunodeficiency gene is modified, e.g., knocked out, to produce an immunodeficient animal which can then be used for a number of purposes relating to modeling and quantifying a particular type of immunodeficiency. Such an animal may be also be used to model xenografting and tumorigenesis. It should be recognized that genetically modified animals as described herein, such as rats, are likely to exhibit certain characteristics exhibited in the corresponding mouse models in which an immunodeficiency gene altered. Such characteristics include certain disorders of the skin, nails and hair including hairlessness, abnormal skin pigmentation (Rag1, FoxN1), and increased susceptibility to skin cancers and psoriasis (FoxN1). In a genetically modified animal as described herein and which exhibits a phenotype comparable to that observed in mouse models, the animal can provide a new and useful model for studying the underlying causes of alopecia, vitiligo, melanogenesis, or psoriasis.

[0104] A genetically modified animal as described herein, such as a rat produced by knocking out any one or more immunodeficiency genes such as any one or more of Rag1, Rag2, FoxN1, and DNAPK, such that the animal does not express the target gene(s), may exhibit an enhanced engraftment capacity of heterologous cells relative to a wild type animal, may have either non-functional T-cells or non-functional B-cells, or may have no T-cells or B-cells, or may exhibit reduced macrophage function relative to a wild type rat, or may exhibit no NK cells or NK cell activity, or exhibits reduced dendritic cell (DC) function relative to a wild type animal, and retains human tumor cells. Such an animal may be used for example in a method of screening an antiviral agent, wherein the effects of exposure of the genetically modified animal to the antiviral agent can be measured and compared to those observed in a wild type control animal. Such an animal may be used to develop a diagnostic assay for an immunodeficiency including a leukemia, in which the animal, either left untreated or previously treated with a therapeutic agent, is assessed for the presence of one or more biomarkers relative a non-affected control animal. Such an animal may be used in a method of screening a candidate therapy or therapeutic compound for treating leukemia, for example, using a genetically modified animal in which any one or more immunodeficiency genes such as Rag1, Rag2, FoxN1, or DNAPK are knocked out, and the animal, either left untreated or previously treated with a therapeutic agent which may be a drug, microbe, transplanted cells, or other agent, is then treated with the candidate therapy or candidate therapeutic agent, a biological sample is obtained from the animal, and the biological sample evaluated relative to a sample from a non-affected wild-type control sample, or a sample not subjected to the candidate therapy or therapeutic agent.

[0105] A method for modeling an autoimmune disease may involve adoptive transfer of B cells reacting to an antigen for an autoimmune disease, or T cells activated for an autoimmune disease. The appropriate non-human mammal with the antigen target of the autoimmune disease can be immunized as follows: immune cells are prepared from the immunized animal, the immune cells are transplanted to genetically modified animal as described herein such as a Rag1, Rag2, FoxN1, or DNAPK knockout rat, or a rat with any combination of these genes knocked out, and development of autoimmune phenotypes in the recipient is evaluated as compared to either a non-transplanted knockout animal, or compared to a knockout animal transplanted with non-pathologic immune cells that lack auto-reactivity, or compared to a wild type animal transplanted with immune cells as described above.

[0106] A method of evaluating potential therapeutic agents for skin disorders involving pigmentation (melanocyte biology), hypersensitivity to ultraviolet (uv) light damage, hair development, nail disease (onychocyte differentiation), or psoriasis, can include: identifying traits indicating skin disorders in a genetically modified animal as described herein, such as in a rat in which one or more of FoxN1, Rag1, Rag2, or DNAPK are knocked out, as compared to wild-type controls, including: hypopigmentation, increased incidence of
skin cancers, lack of hair, brittle or dysmorphic nails, or psoriatic lesions; treating the genetically modified animal with a candidate therapeutic compound; and evaluating any change in phenotype as compared to untreated knockout animals or knockout animals mock-treated as a control. A change in phenotype such as increased pigmentation, decreased sensitivity to UV light, increased hair development, normal nail development, or improvement or healing of psoriatic lesions is indicative of a therapeutic effect of the indicates the candidate compound is a therapeutic agent.

[0107] A method for creating a combined immunodeficiency syndrome model may include providing a genetically modified animal such as a rat wherein Rag1, Rag2, FoxN1, or DNAPK are knocked out as described herein, and the knockout animal is further rendered deficient for natural killer (NK) cells by any of one or several possible methods, including, or example, i) disruption of the Lyst gene; or ii) treatment of FoxN1 mutant animals with a compound that inhibits NK cell activity, for example: NSAIDs (non-steroidal anti-inflammatory drugs), statins, allosertic LFA-1 inhibitors, vinblastine, paclitaxel, docetaxel, cladribine, chlorambucil, bortezomib, or MG-132.

DEFINITIONS

[0108] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0109] A “gene,” as used herein, refers to a DNA region (including exons and introns) encoding a gene product, as well as all DNA regions which regulate the production of the gene product, whether or not such regulatory sequences are adjacent to coding and/or transcribed sequences. Accordingly, a gene includes, but is not necessarily limited to, promoter sequences, terminators, translational regulatory sequences such as ribosome binding sites and internal ribosome entry sites, enhancers, silencers, insulators, boundary elements, replication origins, matrix attachment sites, and locus control regions.

[0110] The terms “nucleic acid” and “polynucleotide” refer to a deoxyribonucleotide or ribonucleotide polymer, in linear or circular conformation, and in either single- or double-stranded form. For the purposes of the present disclosure, these terms are not to be construed as limiting with respect to the length of a polymer. The terms can encompass known analogs of natural nucleotides, as well as nucleotides that are modified in the base, sugar and/or phosphate moieties (e.g., phosphorothioate backbones). In general, an analog of a particular nucleotide has the same base-pairing specificity; i.e., an analog of A will base-pair with T.

[0111] The terms “polypeptide” and “protein” are used interchangeably to refer to a polymer of amino acid residues.

[0112] The term “recombination” refers to a process of exchange of genetic information between two polynucleotides. For the purposes of this disclosure, “homologous recombination” refers to the specialized form of such exchange that takes place, for example, during repair of double-strand breaks in cells. This process requires sequence similarity between the two polynucleotides, uses a “donor” or “exchange” molecule to template repair of a “target” molecule (i.e., the one that experienced the double-strand break), and is variously known as “non-crossover gene conversion” or “short tract gene conversion,” because it leads to the transfer of genetic information from the donor to the target. Without being bound by any particular theory, such transfer can involve mismatch correction of heteroduplex DNA that forms between the broken target and the donor, and/or “synthesis-dependent strand annealing,” in which the donor is used to resynthesize genetic information that will become part of the target, and/or related processes. Such specialized homologous recombination often takes place in an altered form of the sequence of the target molecule such that part or all of the sequence of the donor polynucleotide is incorporated into the target polynucleotide. As used herein, the terms “target site” or “target sequence” refer to a nucleic acid sequence that defines a portion of a chromosomal sequence to be edited and to which a zinc finger nuclease is engineered to recognize and bind, provided sufficient conditions for binding exist.

[0113] Techniques for determining nucleic acid and amino acid sequence identity are known in the art. Typically, such techniques include determining the nucleotide sequence of the mRNA for a gene and/or determining the amino acid sequence encoded thereby, and comparing these sequences to a second nucleotide or amino acid sequence. Genomic sequences can also be determined and compared in this fashion. In general, identity refers to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Two or more sequences (polynucleotide or amino acid) can be compared by determining their percent identity. The percent identity of two sequences, whether nucleic acid or amino acid sequences, is the number of exact matches between the two aligned sequences divided by the length of the shorter sequences and multiplied by 100. An approximate alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman, Advances in Applied Mathematics 2:482-489 (1981). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff, Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA, and normalized by Gribkov, Nucl. Acids Res. 14(6):6745-6765 (1986). An exemplary implementation of this algorithm to determine percent identity of a sequence is provided by the Genetics Computer Group (Madison, Wis.) in the “BestFit” utility application. Other suitable programs for calculating the percent identity or similarity between sequences are generally known in the art, for example, another alignment program is BLAST, used with default parameters. For example, BLASTN and BLASTP can be used using the following default parameters: genetic code=standard; filter=none; strand=both; cutoff=60; expect=10; Matrix=BLOSUM62; Descriptions=50 sequences; sort by =HIGH SCORE; Databases=non-redundant, GenBank+EMBL+DDBJ+PDB+GenBank CDS translations+F5Swiss protein+F5uniprot+PIR. Details of these programs can be found on the GenBank website. With respect to sequences described herein, the range of desired degrees of sequence identity is approximately 80% to 100% and any integer value therebetween. Typically the percent identities between sequences are
at least 70-75%, preferably 80-82%, more preferably 85-90%, even more preferably 92%, still more preferably 95%, and most preferably 98% sequence identity.

[0114] Alternatively, the degree of sequence similarity between polynucleotides can be determined by hybridization of polynucleotides under conditions that allow formation of stable duplexes between regions that share a degree of sequence identity, followed by digestion with single-stranded-specific nucleases, and size determination of the digested fragments. Two nucleic acid, or two polypeptide sequences are substantially similar to each other when the sequences exhibit at least about 70%-75%, preferably 80%-82%, more-preferably 85%-90%, even more preferably 92%, still more preferably 95%, and most preferably 98% sequence identity over a defined length of the molecules, as determined using the methods above. As used herein, substantially similar also refers to sequences showing complete identity to a specified DNA or polypeptide sequence. DNA sequences that are substantially similar can be identified in a Southern hybridization experiment under, for example, stringent conditions, as defined for that particular system. Defining appropriate hybridization conditions is within the skill of the art. See, e.g., Sambrook et al., supra; Nucleic Acid Hybridization: A Practical Approach, editors B. D. Hames and S. J. Higgins, (1985) Oxford; Washington, D.C.; IRL Press).

[0115] Selective hybridization of two nucleic acid fragments can be determined as follows. The degree of sequence identity between two nucleic acid molecules affects the efficiency and strength of hybridization events between such molecules. A partially identical nucleic acid sequence will at least partially inhibit the hybridization of a completely identical sequence to a target molecule. Inhibition of hybridization of the completely identical sequence can be assessed using hybridization assays that are well known in the art (e.g., Southern (DNA) blot, Northern (RNA) blot, solution hybridization, or the like, see Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, (1989) Cold Spring Harbor, N.Y.). Such assays can be conducted using varying degrees of selectivity, for example, using conditions varying from low to high stringency. If conditions of low stringency are employed, the absence of non-specific binding can be assessed using a secondary probe that lacks even a partial degree of sequence identity (for example, a probe having less than about 30% sequence identity with the target molecule), such that, in the absence of non-specific binding events, the secondary probe will not hybridize to the target.

[0116] When utilizing a hybridization-based detection system, a nucleic acid probe is chosen that is complementary to a reference nucleic acid sequence, and then by selection of appropriate conditions the probe and the reference sequence selectively hybridize, or bind, to each other to form a duplex molecule. A nucleic acid molecule that is capable of hybridizing selectively to a reference sequence under moderately stringent hybridization conditions typically hybridizes under conditions that allow detection of a target nucleic acid sequence of at least about 10-14 nucleotides in length having at least approximately 70% sequence identity with the sequence of the selected nucleic acid probe. Stringent hybridization conditions typically allow detection of target nucleic acid sequences of at least about 10-14 nucleotides in length having a sequence identity of greater than about 90-95% with the sequence of the selected nucleic acid probe. Hybridization conditions useful for probe/reference sequence hybridization, where the probe and reference sequence have a specific degree of sequence identity, can be determined as is known in the art (see, for example, Nucleic Acid Hybridization: A Practical Approach, editors B. D. Hames and S. J. Higgins, (1985) Oxford; Washington, D.C.; IRL Press). Conditions for hybridization are well-known to those of skill in the art.

[0117] Hybridization stringency refers to the degree to which hybridization conditions disfavor the formation of hybrids containing mismatched nucleotides, with higher stringency correlated with a lower tolerance for mismatched hybrids. Factors that affect the stringency of hybridization are well-known to those of skill in the art and include, but are not limited to, temperature, pH, ionic strength, and concentration of organic solvents such as, for example, formamide and dimethylsulfoxide. As is known to those of skill in the art, hybridization stringency is increased by higher temperatures, lower ionic strength and lower solvent concentrations. With respect to stringency conditions for hybridization, it is well known in the art that numerous equivalent conditions can be employed to establish a particular stringency by varying, for example, the following factors: the length and nature of the sequences, base composition of the various sequences, concentrations of salts and other hybridization solution components, the presence or absence of blocking agents in the hybridization solutions (e.g., dextran sulfate, and polyethylene glycol), hybridization reaction temperature and time parameters, as well as, varying wash conditions. A particular set of hybridization conditions may be selected following standard methods in the art (see, for example, Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition, (1989) Cold Spring Harbor, N.Y.).

EXAMPLES

[0118] The following non-limiting examples are included to illustrate the invention.

Example 1

Identification of ZFNs that Edit the Rag1 Locus

[0119] The Rag1 gene was chosen for zinc finger nuclease (ZFN) mediated genome editing. ZFNs were designed, assembled, and validated using strategies and procedures previously described (see Geurts et al. Science (2009) 325:433). ZFN design made use of an archive of pre-validated 1-finger and 2-finger modules. The rat Rag1 gene region (XM_001079242) was scanned for putative zinc finger binding sites to which existing modules could be fused to generate a pair of 4-, 5-, or 6-finger proteins that would bind a 12-18 by sequence on one strand and a 12-18 by sequence on the other strand, with about 5-6 by between the two binding sites.

[0120] Capped, polyadenylated mRNA encoding each pair of ZFNs was produced using known molecular biology techniques. The mRNA was transfected into rat cells. Control cells were injected with mRNA encoding GFP. Active ZFN pairs were identified by detecting ZFN-induced double strand chromosomal breaks using the Cel-1 nuclease assay. This assay detects alleles of the target locus that deviate from wild type as a result of non-homologous end joining (NHEJ)-mediated imperfect repair of ZFN-induced DNA double strand breaks. PCR amplification of the targeted region from a pool of ZFN-treated cells generates a mixture of WT and mutant amplicons. Melting and reannealing of this mixture results in mismatches forming between heteroduplexes of the WT and mutant alleles. A DNA “bubble” formed at the site of mismatch is cleaved by the surveyor nuclease Cel-1, and the
cleavage products can be resolved by gel electrophoresis. This assay revealed that the ZFN pair targeted to bind 5'-ttCCTGAGGAGAATgag-gaggtctac-3' (SEQ ID NO: 5; contact sites in uppercase) and 5'-gtCACGAGGAGAATgag-gaggtctac-3' (SEQ ID NO: 6) cleaved within the Rag1 locus.

**Example 2**

**Editing the Rag1 Locus**

Capped, polyadenylated mRNA encoding the active pair of ZFNs was microinjected into fertilized rat embryos using standard procedures (e.g., see Geurts et al. (2009) supra). The injected embryos were either incubated in vitro, or transferred to pseudopregnant female rats to be carried to parturition. The resulting embryos/fetus, or the toe/tail clip of live born animals were harvested for DNA extraction and analysis. DNA was isolated using standard procedures. The targeted region of the Rag1 locus was PCR amplified using appropriate primers. The amplified DNA was subcloned into a suitable vector and sequenced using standard methods. Fig. 1 presents DNA sequences of edited Rag1 loci in two animals. One animal had a 808 by deletion in exon 2, and a second animal had a 29 by deletion in the target sequence of exon 2. These deletions disrupt the reading frame of the Rag1 coding region.

**Example 3**

**Identification of ZFNs that Edit the Rag2 Locus**

ZFNs that target and cleave the Rag2 gene were identified essentially as described above. The rat Rag2 gene (XM_001079235) was scanned for putative zinc finger binding sites. ZFNs were assembled and tested essentially as described in Example 1. This assay revealed that the ZFN pair targeted to bind 5'-tgAAGGCGACatgag-gaggtctac-3' (SEQ ID NO: 9; contact sites in uppercase) and 5'-cgAGGCGACatgag-gaggtctac-3' (SEQ ID NO: 10); and a second pair targeted to bind 5'-tgGCTGATTTTGAAAGGAGGGCCagggc-3' (SEQ ID NO: 11) and 5'-atGAGGAGGAGCGTGCAGaatgagggaa-3' (SEQ ID NO: 12)

**Example 4**

**Editing the Rag2 Locus**

Rat embryos were microinjected with mRNA encoding the active pair of Rag2 ZFNs essentially as described in Example 2. The injected embryos were incubated and DNA was extracted from the resultant animals. The targeted region of the Rag2 locus was PCR amplified using appropriate primers. The amplified DNA was subcloned into a suitable vector and sequenced using standard methods. Fig. 2 presents DNA sequences of edited Rag2 loci in two animals. One animal had a 13 by deletion in the target sequence in exon 3, and a second animal had a 2 by deletion in the target sequence of exon 3. These deletions disrupt the reading frame of the Rag2 coding region.

**Example 5**

**Identification of ZFNs that Edit the FoxN1 Locus**

ZFNs that target and cleave the FoxN1 gene were identified essentially as described above in Example 1. The rat FoxN1 gene (XM_220632) was scanned for putative zinc finger binding sites. ZFNs were assembled and tested essentially as described in Example 1. This assay revealed two pairs of active ZFNs that cleaved within the FoxN1 locus: a first pair targeted to bind 5'-tgAAGGCGATGAAGAgatgag-gaggtctac-3' (SEQ ID NO: 9; contact sites in uppercase) and 5'-cgAAGGCGATGAAGAgatgag-gaggtctac-3' (SEQ ID NO: 10); and a second pair targeted to bind 5'-tgGCTGATTTTGAAAGGAGGGCGagggc-3' (SEQ ID NO: 11) and 5'-atGAGGAGGAGCGTGCAGaatgagggaa-3' (SEQ ID NO: 12)
SEQUENCE LISTING

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212> TYPE: DNA
213> ORGANISM: Rattus rattus

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210> SEQ ID NO 2
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212> TYPE: DNA
213> ORGANISM: Rattus rattus

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ggaagagaca tccgccccac tgcagcgtca gcagaaaaact aaaaactgtg ctcaacccatg 180
cgtacacgga ctgcgtcgaag 200

210> SEQ ID NO 3
211> LENGTH: 300
212> TYPE: DNA
213> ORGANISM: Rattus rattus

400> SEQUENCE: 3

tatcatacgc ggggaaaa ca gccaacaaaa tggagtttcc gataaagtt atacactagc 60
tgcctggtgc aagaacaaca aaaaagttac tttcggtgtg agagaaag aattagtagg 120
agatgttcct gaagccagat atgcaccttc cattagctg gtataagcc gggaaaaag 180
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tgctggctt cttctttgag gacggtcata catgctctct acccaagaa ccacagaaa 240
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SEQUENCE: 10

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SEQ ID NO 11
LENGTH: 28
TYPE: DNA
ORGANISM: Rattus rattus

SEQUENCE: 11

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SEQ ID NO 12
LENGTH: 28
TYPE: DNA
ORGANISM: Rattus rattus

SEQUENCE: 12

atgcaggaag agtgtcagaa gttggaaga

SEQ ID NO 13
LENGTH: 28
TYPE: DNA
ORGANISM: Rattus rattus

SEQUENCE: 13

tacacaagtc ttctccagg agcttga

SEQ ID NO 14
LENGTH: 28
TYPE: DNA
ORGANISM: Rattus rattus

SEQUENCE: 14

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SEQ ID NO 15
LENGTH: 35
TYPE: PRT
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: SYNTHESIZED

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Leu Lys Asp
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SEQ ID NO 16
LENGTH: 35
TYPE: PRT
ORGANISM: Artificial Sequence

FEATURE:
OTHER INFORMATION: SYNTHESIZED

SEQUENCE: 16

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Arg Ile Asn

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Glu Ser Leu Asn Ala Thr Ser Ser Asn Leu Ser Arg Asp Arg Ser Ser  
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Arg Lys Arg  
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Gln Ser Gly Ser Leu Thr Arg Gln Ser Ser Asp Leu Arg Arg Gln Arg  
1 5 10 15

Thr His Leu Thr Gln Ser Gly His Leu Gln Arg Gln Ser Gly Asp  
20 25 30

Leu Thr Arg  
35

<210> SEQ ID NO 23
<211> LENGTH: 35
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: SYNTHESIZED

<400> SEQUENCE: 23

Gln Ser Gly Asp Leu Thr Arg Ser Ser Ser Asp Arg Lys Lys Asp Ser  
1 5 10 15

Ser Asp Arg Lys Lys Arg Ser Aon Leu Ser Thr Asp Asn Ser Asn  
20 25 30

Arg Ile Asn  
35

<210> SEQ ID NO 24
<211> LENGTH: 35
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<220> FEATURE:
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Thr Ser Gly His Leu Ser Arg Gln Ser Gly Asn Leu Ala Arg His Leu
What is claimed is:

1. A genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein.

2. The genetically modified animal of claim 1, wherein the edited chromosomal sequence is inactivated, modified, or comprises an integrated sequence.

3. The genetically modified animal of claim 1, wherein the edited chromosomal sequence is inactivated such that no functional immunodeficiency-associated protein is produced.

4. The genetically modified animal of claim 3, wherein the inactivated chromosomal sequence comprises no exogenously introduced sequence.

5. The genetically modified animal of claim 3, further comprising at least one chromosomally integrated sequence encoding a functional immunodeficiency protein.

6. The genetically modified animal of claim 1, wherein the immunodeficiency protein is chosen from RAG1, RAG2, DNAPK AND FOXL1, and combinations thereof.

7. The genetically modified animal of claim 1, further comprising a conditional knock-out system for conditional expression of the immunodeficiency protein.

8. The genetically modified animal of claim 1, wherein the edited chromosomal sequence comprises an integrated reporter sequence.

9. The genetically modified animal of claim 1, wherein the animal is heterozygous or homozygous for the at least one edited chromosomal sequence.

10. The genetically modified animal of claim 1, wherein the animal is an embryo, a juvenile, or an adult.

11. The genetically modified animal of claim 1, wherein the animal is chosen from bovine, canine, equine, feline, ovine, porcine, non-human primate, and rodent.

12. The genetically modified animal of claim 1, wherein the animal is rat.

13. The genetically modified animal of claim 12, wherein the animal is rat and the protein is an ortholog of a human immunodeficiency protein.

14. A non-human embryo, the embryo comprising at least one RNA molecule encoding a zinc finger nuclease that recognizes a chromosomal sequence encoding an immunodeficiency protein, and, optionally, at least one donor polynucleotide comprising a sequence encoding an immunodeficiency protein.

15. The non-human embryo of claim 14, wherein the immunodeficiency protein is chosen from RAG1, RAG2, DNAPK AND FOXL1, and combinations thereof; and the embryo is chosen from bovine, canine, equine, feline, ovine, porcine, non-human primate, and rodent.

16. The non-human embryo of claim 15, wherein the zinc finger nuclease comprises a DNA binding domain that binds a sequence having at least about 80% sequence identity to a sequence chosen from SEQ ID NOS: 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14.

17. The non-human embryo of claim 15, wherein the embryo is rat and the protein is an ortholog of the human immunodeficiency protein.

18. A genetically modified cell, the cell comprising at least one edited chromosomal sequence encoding an immunodeficiency protein.

19. The genetically modified cell of claim 18, wherein the edited chromosomal sequence is inactivated, modified, or comprises an integrated sequence.

20. The genetically modified cell of claim 18, wherein the edited chromosomal sequence is inactivated such that no functional immunodeficiency-associated protein is produced.

21. The genetically modified cell of claim 20, wherein the inactivated chromosomal sequence comprises no exogenously introduced sequence.

22. The genetically modified cell of claim 20, further comprising at least one chromosomally integrated sequence encoding a functional immunodeficiency protein.

23. The genetically modified cell of claim 18, wherein the immunodeficiency protein is chosen from RAG1, RAG2, DNAPK AND FOXL1, and combinations thereof.

24. The genetically modified cell of claim 18, further comprising a conditional knock-out system for conditional expression of the immunodeficiency protein.

25. The genetically modified cell of claim 18, wherein the edited chromosomal sequence comprises an integrated reporter sequence.

26. The genetically modified cell of claim 18, wherein the immunodeficiency protein is chosen from RAG1, RAG2, DNAPK AND FOXL1, and combinations thereof; and the cell is chosen from bovine, canine, equine, feline, human, ovine, porcine, non-human primate, or rodent origin.

27. The genetically modified cell of claim 19, wherein the cell is heterozygous or homozygous for the at least one edited chromosomal sequence.

28. The genetically modified cell of claim 19, wherein the cell is rat origin and the protein is an ortholog of a human immunodeficiency protein.

29. A method for assessing the effect of an agent in an animal, the method comprising contacting a genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein with an agent, and comparing results of a selected parameter to results obtained from contacting a wild-type animal with the same agent, wherein the selected parameter is chosen from:

a) rate of elimination of the agent or its metabolite(s);

b) circulatory levels of the agent or its metabolite(s);

c) bioavailability of the agent or its metabolite(s);

d) rate of metabolism of the agent or its metabolite(s);

e) rate of clearance of the agent or its metabolite(s);
f) toxicity of the agent or its metabolite(s); and
g) efficacy of the agent or its metabolite(s).

30. The method of claim 29, wherein the agent is a pharmaceutically active ingredient, a drug, a toxin, or a chemical.

31. The method of claim 29, wherein the at least one edited chromosomal sequence is inactivated such that the immunodeficiency protein is not produced, and wherein the animal further comprises at least one chromosomally integrated sequence encoding an ortholog of the immunodeficiency protein.

32. The method of claim 29, wherein the immunodeficiency protein is chosen from RAG1, RAG2, DNAPK AND FOXN1, and combinations thereof.

33. The method of claim 29, wherein the animal is a rat of a strain chosen from Dahl Salt-Sensitive, Fischer 344, Lewis, Long Evans Hooded, Sprague-Dawley, and Wistar.

34. A method for assessing the therapeutic potential of an agent in an animal, the method comprising contacting a genetically modified animal comprising at least one edited chromosomal sequence encoding an immunodeficiency protein with an agent and comparing results of a selected parameter to results obtained from a wild-type animal with no contact with the same agent, wherein the selected parameter is chosen from:

a) spontaneous behaviors;
b) performance during behavioral testing;
c) physiological anomalies;
d) abnormalities in tissues or cells;
e) biochemical function; and
f) molecular structures.

35. The method of claim 34, wherein the agent is a pharmaceutically active ingredient, a drug, a toxin, or a chemical.

36. The method of claim 34, wherein the at least one edited chromosomal sequence is inactivated such that the immunodeficiency protein is not produced, and wherein the animal further comprises at least one chromosomally integrated sequence encoding an ortholog of the immunodeficiency protein.

37. The method of claim 34, wherein the immunodeficiency protein is chosen from RAG1, RAG2, DNAPK AND FOXN1, and combinations thereof.

38. The method of claim 34, wherein the animal is a rat chosen from Dahl Salt-Sensitive, Fischer 344, Lewis, Long Evans Hooded, Sprague-Dawley, and Wistar.

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